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Are miRNAs critical determinants in Herpes Simplex Virus pathogenesis?

Siddheshvar Bhela[1] and **Barry T. Rouse**[1]

[1]Department of Biomedical and Diagnostic Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN

Abstract

miRNAs are small noncoding RNA that play a crucial role in gene regulation by inhibiting translation or promoting mRNA degradation. Viruses themselves express miRNAs that can target either the host or viral mRNA transcriptome. Moreover, viral infection of cells causes a drastic change in host miRNAs. This complex interaction between the host and viruses often favors the virus to evade immune elimination and favors the establishment and maintenance of latency. In this review we discuss the function of both host and viral miRNAs in regulating herpes simplex virus pathogenesis and also discuss the prospect of using miRNAs as biomarkers and therapeutic tools.

Keywords

microRNAs; Herpes Simplex Virus (HSV); Herpes Simplex Keratitis (HSK); Herpes Simplex Encephalitis (HSE); Latency; Resolution; Therapy

1. Introduction

We became initially aware of microRNA (miRNA) from studies with nematodes [1], but now know these nucleic acids play a crucial gene regulatory role in all eukaryotes so far investigated [2]. They also occur in bacteria and in complex viral pathogens [3]. The miRNA tally in mammalian cells exceeds 1000 and dysregulation of one or more species can impact on the outcome of both infectious and non-infectious diseases. Host well adapted pathogens such as herpes simplex virus (HSV) employ numerous miRNA both to regulate their own replication events as well as to manage interaction of the virus within the host [4]. Of particular relevance miRNA of both virus and host help dictate the type of interaction that occurs. With herpes viruses, these can include productive replication, latency or inflammatory lesions and some herpes viruses miRNA can also influence whether or not neoplasia occurs [5]. The purpose of this review is to describe situations with HSV, which are affected by expression levels of one or more species of miRNA. We will also evaluate

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the question as to the value of monitoring miRNA levels for diagnosis and prognosis as well as their potential value in the therapy of herpetic infections.

2. Models available to evaluate miRNA involvement

miRNA processing and its ability to exert its effects requires key genes such as Dicer, DGCR8 and Ago2. Global deletion of any of these genes in mice leads to death or severe developmental defects during birth [6-8]. Thus, to study the effects of loss of miRNA in individual cell types cre-inducible conditional knockouts were generated [9-11]. Although this permitted the evaluation of the role of total miRNAs in development and in tissues, the role of individual miRNAs in observed phenotypes remained unknown. In order to study this, individual miRNAs were knocked out from mice with the cre-inducible conditional knockouts the most valuable approach [12]. miRNA over expression could also be studied in a global, a tissue or cell specific manner by making miRNA transgenic mice [13-15]. More recently mouse models of doxycycline inducible miRNA knockouts have also been developed where the administration of tamoxifen allowed for the deletion or overexpression of miRNA of interest [16, 17, 13]. Lastly, of of therapeutic interest, another way to regulate miRNA activity both in-vitro and in-vivo is the use of chemically modified antagomirs and miRNA mimics delivered in nanoparticles, which is discussed in detail in a later section.

3. Role of miRNA in HSV replication

miRNAs play vital roles in virus-host interaction with both viral miRNAs and cellular miRNAs regulating HSV replication. Viral miRNAs auto-regulate viral mRNAs and they also down-regulate host mRNAs. This serves to facilitate evasion by the virus from the host defense system. Host miRNAs also play a crucial role in virus replication because host miRNA expression profiles change noticeably during virus infection. Below we discuss how cellular and viral miRNAs regulate HSV replication.

3.1 Cellular miRNAs regulating HSV replication

Cellular miRNAs can affect HSV virus replication either via direct binding to the HSV virus genome, or through virus-mediated changes in the host transcriptome. For example, Zhou et al. showed that miR-649 downregulation in HSV-1 infected HeLa cells [18] led to increased expression of its target MALT1 that results in inhibition of viral replication by activating the NFkb signaling pathway. Another report by Wang et al. showed that ICP4, an immediate early gene of HSV-1, could directly bind to the miR-101 promoter to activate its expression [19]. The increased miR-101 led to downregulation of its target GRSF1 which in turn increased HSV-1 replication by binding to HSV-1 p40 mRNA and promoting its expression. Thus ICP4 induced miR-101 attenuates HSV-1 replication. Another group showed that miR-101 could also target the mitochondrial ATP synthase subunit beta (ATP5B), a cellular protein that reduces HSV-1 replication [20]. Thus, miR-101 could target multiple host factors that help in attenuating HSV-1 replication. The same group also showed that HSV-1 infection of HeLa cells led to upregulation of miR-23a, which then caused downregualtion of IRF1, a gene involved in innate antiviral immunity of the cell [21]. Taken together these reports suggest that cellular miRNAs play a critical role in determining the outcome of HSV

replication either by targeting host or viral mRNA transcripts. Modulating the expression of these cellular miRNAs could be used to our advantage to reduce HSV replication.

3.2 Viral miRNA regulating HSV replication

Similar to cellular miRNAs, viral miRNAs can also target virus transcripts or host cellular transcripts and both affect HSV replication. Accordingly, HSV-miR-H6, which is most abundant during productive HSV-1 infection, inhibits viral replication by targeting the viral immediate early gene ICP4 in human corneal epithelial cells [22]. Another viral HSV-miRNA, H-27, targets the cellular transcriptional repressor Kelch-like 24 (KLHL24), which inhibits transcriptional efficiency of viral immediate early and early genes [22]. This mechanism allowed HSV-1 to promote replication and proliferation and to evade the cellular immune response.

Thus we can conclude that herpes viruses have developed many mechanisms to regulate their own replication. These might also help them to evade immune responses and establish latency, a topic discussed next.

4. Role of miRNAs in HSV-1 latency

HSV-1 can adopt a second relationship with the host, namely that of latency. This occurs mainly in cells of the nervous system and is a situation where virus fails to complete the productive replication cycle, but instead undergoes alternative molecular events referred to as latency. Usually during latency no viral encoded proteins are expressed, but latently infected cells express a transcript LAT, not found during productive replication. LAT does encode some viral miRNAs and these are likely involved in the establishment, maintenance and reactivation of latency.

4.1 Viral miRNAs regulating latency

HSV-1 and HSV-2 LAT encodes several different viral miRNAs and were first discovered in 2006 by the Coen group [23]. Although, the function of the majority of the HSV-viral miRNAs is still unknown, some of the miRNAs influence the generation, maintenance or reactivation from latency. For example, Jiang et al. generated a HSV H2 mutant virus where HSV-miR-H2 was disrupted [24]. Mice ocularly infected with the H2 mutant virus exhibited increased mortality compared to the control WT virus. The increased mortality was attributed to increased rate of reactivation from latency in the TG of the H2 mutant virus compared to the WT virus infected TG. The mechanism of action appeared to result from HSV-miR-H2 targeting the immediate early gene ICP0. Thus an explanation for the increased neuro-virulence observed by the H2 mutant virus could be due to increased levels of ICP0 leading to reactivation from latency.

Of additional interest, herpes viral miRNA HSV-miR-H6 is expressed during latency and plays a role in reactivation from latency [25]. To study the role of miR-H6 in-vivo, Tang et al generated a mutant virus which abrogated miR-H6 expression, but did not affect levels of HSV-2 LAT or viral DNA copy numbers. Interestingly, ocular infection of mice and vaginal infection of guinea pigs with the H6 mutant virus did not show any differences in the establishment of viral latency compared to WT virus. However, guinea pigs infected with the

H6 mutant virus showed reduced neurological complications compared to the WT virus. The mechanism for this phenomenon remains unknown and could be due to either viral HSV-miR-H6 targeting the host or viral transciptome.

4.2 Cellular miRNAs regulating HSV latency

Other than viral miRNAs, cellular miRNAs may also influence the establishment maintenance and reactivation from latency. One such candidate in miR-155. Thus, miR-155KO mice were susceptible to herpes simplex encephalitis [26]. This was explained by defective CD8 T cell responses in miR-155KO mice. CD8 T cell responses are required for protection of the CNS and PNS from HSV-1 infection [27, 28]. Additionally, the defective CD8 T cell responses contributed to increased ex-vivo reactivation from the latently infected TG of miR-155KO mice (90% reactivation vs 15% in WT) [26]. Although the molecular mechanism for defective CD8 T cell responses after HSV-1 infection in the miR-155KO mice were not investigated, reports of others do provide some insight. Accordingly, Gracias et al. showed that miR-155KO CD8 T cells show increased type1 IFN signaling and consequently anti-proliferative effects [29].

Another report, which is also discussed in the next section, showed that that host cellular miR-138 can regulate HSV-1 latency. Accordingly, Pan et al (30) found that neurons express miR-138, which targets ICP0, a viral trans-activator of lytic gene expression. This promotes host survival and HSV-1 viral latency. They showed that a mutant HSV-1 (M138) with disrupted miR-138 target sites in ICP0 mRNA exhibited enhanced expression of ICP0. Moreover, increased lytic transcripts in TG during the establishment of latency resulted in increased mortality and encephalitis symptoms [30].

Taken together, herpes viruses have evolved strategies that allows them to establish lifelong latency in the host. Importantly, the interplay between viral miRNAs and cellular miRNAs seems to play a pivotal role in the establishment, maintenance, and reactivation of the virus from latency. Therefore, targeting HSV miRNAs may constitute a new and different approach to antiviral therapy.

5. Role of miRNA during acute HSV-1 infection

Herpes simplex viruses 1 and 2 can be a cause of acute encephalitis with an incidence rate of 2–4 individuals/million annually [31-33]. In adults, the usual virus involved is HSV-1 and most commonly it occurs for unknown reasons in those experiencing virus reactivation in the peripheral ganglion. Treatment includes high doses of intravenous acyclovir or other antivirals, but 20% of the affected patients are left with neurological sequelae [34]. The underlying processes that drive herpes simplex encephalitis (HSE) seem to involve both direct effects of the virus as well as bystander damage by a host response to the infection [35-37]. It is conceivable that miRNAs expressed by the cells of the CNS or the immune system could influence the susceptibility of these cells to viral infection and also contributes to the inflammation associated with encephalitis. Currently, the involvement of miRNAs in HSE is still in its infancy and needs to be further investigated. However, it is becoming increasingly evident that several miRNAs play a critical role in the innate immune response of CNS resident cells, which is required for lytic viral clearance of HSV [38]. CNS resident

cells such as microglia, neurons and astrocytes possess TLR activity and participate in viral clearance by secreting various effector molecules such as type I interferons and effector cytokines [39]. Additionally, an exacerbated innate immune response could also contribute to HSE [36]. Since miRNA can affect the function of CNS resident cells, it is conceivable that miRNA influence the outcome of HSV-1 infection in the CNS.

Of note there have been a few reports on the role of miRNAs in CNS resident cells during HSE. However, as already mentioned the expression of miR-138 in neurons can help decide between the lytic and latent state of HSV infection (30). Thus, a mutant HSV-1 (M138) with disrupted miR-138 target sites in ICP0 mRNA exhibited enhanced expression of ICP0. This resulted in increased encephalitis symptoms and mortality [30]. Another report found that miR-155, miR-146a and miR-15b were upregulated in the mouse brain after HSE, shown by others to play a critical role in innate immune responses by CNS resident cells [40]. What roles each of these individual miRNAs play in the CNS during HSE pathogenesis remains to be evaluated. In addition, the same group also found that the miR-200 family and miR-182 cluster were also upregulated in the brain after HSE, particularly in neurons [40]. The suggested mechanism was that miR-200/182 could affect the pathogenesis of HSE by targeting Sdc2, which codes for a cell surface heparan sulfate proteoglycan involved in HSV-1 cellular attachment and entry. Further studies involving miRNA knockout mice would need to be done to confirm the role of these miRNAs in HSE pathogenesis. In addition, of particular interest, there are some reports indicating that humans do have mutations that affect miRNA function or their binding sites in mRNA. These mutations can be pathogenic and contribute to some genetic diseases [41]. It remains to be evaluated whether such mutations might affect the susceptibility of humans to HSV infection of the CNS.

6. Immunopathological consequence of HSV-1 infection

Ocular infection with HSV-1 infection can result in a chronic immunoinflammatory stromal keratitis (SK) lesion that is a significant cause of human blindness. The SK pathogenesis is complex, but it is mainly thought to be a T cell orchestrated inflammatory reaction [42]. Studies in animal models have revealed that these SK lesions are orchestrated mainly by IFN-γ–producing $CD4^+$ T cells (Th1) and, to a lesser extent, by IL-17–producing $CD4^+$ T cells (Th17) [43, 44]. Stromal lesions do not occur in animals that lack T cells, but lesions can be restored with adoptive transfers of CD4+ T cells. The ocular lesion severity is also influenced by regulatory T cells (Treg) as removing or expanding Treg from the onset of lesion induction results in exacerbated or diminished lesions, respectively [45, 46]. Multiple miRNAs are involved in the activation, differentiation, effector function and recruitment of both effector CD4 T cells and Treg [47]. One report has already shown the involvement of one such miRNA, miR-155, in T cell biology and in the pathogenesis of SK lesions [48]. miR-155 is a proinflammatory miRNA which is required for normal immune function. The increased ocular expression of miR-155, which was associated with infection, led to increased Th-1 and Th-17 cell responses, and reduced levels of IFN-γRα and Ship1, which are required for T cell differentiation and function. miR-155KO mice were resistant to developing SK [48]. We were also able to show that anti-155 sequences given in the form of antagomir nanoparticles provided resistance against SK in WT mice [48]. Another report

also showed a role of miR-132 in regulating pathological angiogenesis during SK [49]. miR-132 is upregulted in corneas with corneal neovascularization after SK and likely contributes to angiogenesis by augmenting VEGF signaling via an inhibitory effect on a negative regulator of VEGF function, Ras-GAP. Of therapeutic interest, inhibiting the expression of miR-132 using antagomirs was an effective means of diminishing angiogenesis, as well as reducing the severity of SK [49]. Many other miRNAs were also shown to regulate Th1, Th17 and Treg biology mostly in autoimmune disease settings [50]. Additionally, several other miRNAs were shown to regulate pathogenic angiogenesis in different mouse models [51]. Whether all these miRNAs would similarly affect SK pathogenesis remains to be seen.

In any inflammatory reaction, acute inflammation is protective and is essential to clear invading pathogens. Ideally, it is self-limited and leads to complete resolution of inflammatory infiltrates and clearance of cellular debris so tissues can return to homeostasis, and resolve lesions [52]. Resolution is an active biosynthetic programmed response regulated by specialized pro-resolving mediators (SPM), which include lipoxins, resolvins, protectins and maresins. These SPMs are biosynthesized by inflammatory exudates and have anti-inflammatory (limits further neutrophil infiltration) and pro-resolving (enhancing macrophage clearance of microbial peptides and apoptotic cells) actions [53]. It is now evident that failure of resolution can contribute to ongoing pathogenesis of many chronic inflammatory diseases [53]. It is also becoming evident that SPMs can control inflammation and this was shown by demonstrating that that treating mice with the lipid mediator Resolvin E1 (RVE1), Neuroprotectin D1 (NPD1) and Aspirin-triggered resolvin D1 (AT-RvD1) could promote resolution and reduce the severity of SK lesions [54-56]. New studies have shown that SPMs can modulate several miRNAs involved in the resolution process [57] indicating that modulation of these miRNAs could accelerate resolution and prevent chronic inflammatory disorders such as in SK. We have briefly discussed below some of the relevant miRNAs that might promote resolution.

The Serhan group showed that resolvin (RvD1) administration promoted resolution in part by fine-tuning the levels of several miRNAs. Accordingly, RvD1 binding to its receptor increased miR-21, miR-146b and miR-219 while decreasing miR-208a in tissue-damaging settings [57]. These miRNAs act by changing the expression of several inflammatory mediators. For example, miR-219 targets 3′ UTR of 5-lipoxygenase (enzyme required for the biosynthesis of lipoxins) and reduces leukotriene B4 while increasing SPM production [57]. miR-21 promotes engulfment of apoptotic cells and induces IL-10 production by macrophages during the resolution phase, thus exerting a strong anti-inflammatory effect [58, 59]. miR-146b negatively regulates levels of IL-8 and RANTES, both powerful chemoattractants that recruit leukocytes into inflamed areas [57]. miR-208a regulates NFκβ activation and decreases IL-10 production [57]. We speculate that the provision of SPM during SK may act by inducing the expression of pro-resolution miRNAs that include miR-21, miR-146b, miR-219 and miR-208a. Additionally, providing a cocktail of these miRNA mimics could lead to increased resolution of inflammation. This area merits further investigation.

One miRNA of interest that induces resolution is miR-466l [60]. This miRNA has different functions in different cell types. Thus in neutrophils it seems to promote an acute inflammatory response, however in monocytes and macrophages, it causes the production of SPMs, which promote in turn macrophage phagocytosis and removal of apoptotic PMNs This leads to termination of the inflammatory response [60]. Additionally, miR-466l also promoted macrophage polarization towards a resolution-phase macrophage. miR-466l exerted its action by targeting select ARE-containing targets (ARETs) and lipid mediator biosynthesis [60]. We speculate that this miR-466l might act by increasing acute inflammation during the early stages of SK but later decreased levels may result in chronicity. Thus providing miR-446l during the therapeutic phase might be promising as this might induce resolution and reduce SK lesion severity. This topic needs further investigation.

In conclusion miRNAs are dysregulated during an ongoing inflammatory reaction and this situation could either contribute to pathology, angiogenesis or resolution of inflammation. Thus manipulating miRNAs using antagomirs or miRNA mimics could be a promising therapy to target various events during the pathogenesis of SK.

7. miRNAs as potential biomarkers and therapeutic considerations

The use of miRNAs as biomarkers is an attractive area of research for many reasons. Several studies have already shown that the expression of many miRNAs reflects the underlying pathophysiological processes that are unique in various diseases. miRNAs are also easy to quantify in blood, biological fluids (urine and saliva) [61, 62] and tissue samples using microarray profiling, real-time PCR array, and next-generation sequencing (NGS) technologies. Another advantage of using miRNAs as biomarkers is that they are long-lived in vivo as compared to mRNAs. The increased life of miRNAs could be explained by their increased stability because they may be encased in micro-vesicles such as exosomes. Additionally miRNAs may be released into the extracellular environment bound to Argonaute proteins, which limits degradation [63]. This makes miRNAs resistant to degradation by nucleases. All these factors make miRNAs attractive potential biomarkers. As yet no studies have quantified miRNAs levels as a potential diagnostic or prognostic marker for HSV infection in humans.

It is well established that the expression of miRNAs can be altered in various disease states and that manipulation of these disease-associated miRNAs offers unique opportunities for therapy. Current therapies to downregulate miRNA expression involve the use antagomirs given in nanoparticles, or the use of locked nucleic acid, which are antisense miRNAs that are chemically modified to have higher stability. Similarly to reintroduce miRNA function, miRNA mimics are used. Although a considerable number of preclinical studies involving miRNA therapeutics have been conducted over the years, only miR-122 has moved into clinical development for the treatment of Hepatitis C virus infection [64]. The reason for the majority of miRNA therapeutics being unsuccessful in clinics could be attributed to challenges with regard to delivery, target site accessibility, and off-target effects.

8. Conclusion and perspective

Although the role of miRNAs in HSV pathogenesis is still in its infancy, it is clear that both viral and cellular miRNAs can play a crucial role in many different aspects of herpes virus infections. Additionally, we can surmise that miRNAs can be used as therapeutic tools either by blocking or overexpressing them. Unraveling further the virus/host miRNA networks could produce an answer to the question all herpes virologists wrestle with namely: how to remove herpes virus latency or prevent the virus from reactivating.

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