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Chapter

Herpesviridae and microRNAs

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Abstract

MicroRNAs (miRNAs), first discovered in the year 1993 in the nematode *C. elegans*, are small, approximately 22-nucleotide-long, non-coding RNAs that regulate gene expression. Cellular miRNAs have been implicated in the control of many biological processes, and their dysregulation is associated with different diseases. They can be significantly up/downregulated upon infection or disease, serving as excellent biomarkers and therapeutic targets. Several human DNA viruses, including many herpesviruses, have now been reported to encode viral miRNAs. There are a variety of possible interactions and mechanisms of viral microRNAs (vmiRNAs) which are yet to be remains obscure. Viral miRNAs can function as orthologs of cellular miRNAs and regulate their expression. Additionally, viruses have also developed vmiRNA mechanisms to avoid being targeted by the host miRNAs. Herpes Simplex Viruses (HSV-1 & HSV-2) cause genital and oral herpes, establishing lifelong latent infections in their hosts, and it is one of the most prevalent sexually transmitted infections (STIs) worldwide. vmiRNAs play essential roles in Herpesvirus biology. In this chapter, we will discuss the current knowledge about miRNAs and their role in different stages of Herpesvirus infection. It will also elaborate the biomarkers, therapeutic potential of these molecules, and the prospective areas of future research.

Keywords: Herpesviridae, HSV, miRNA, miRNA biogenesis, HHV, KSHV

1. Introduction

Eight out of the hundred reported herpesviruses, from the family herpesviridae (herpein meaning, "to creep"), cause lytic and latent infections in the humans. The human herpesviruses are classified into the alpha-, beta- and the gamma-herpesviruses, based on the range of hosts they infect. The alpha (α)-herpesviruses, involving the herpes Simplex Virus −1 (HSV-1), HSV-2 and the varicella zoster virus (VZV), are known to infect a broad range of hosts while having a short replication cycle in these hosts. The beta (β)-herpesviruses include the members, the human cytomegalovirus (HCMV) and the reseolo-human herpesvirus −6 and − 7, and infect a restricted range of hosts as compared to the α-herpesviruses while having a longer replication cycle within these hosts. The third group known as the gamma (γ)- herpesviruses, containing the Epstein–Barr virus (EBV) and the Kaposi's sarcoma associated herpesvirus (KSHV), have the most restricted host range amongst the three sub-categories of human herpesviruses [1]. As reported for the year 2016, 13.2% of the global population aged 15 to 49 years were harboring HSV-2 within themselves, whereas about 66.6% amongst the 0 to 49 years aged individuals had HSV-1 infection [2]. Persons infected with HSV-2 are at 3 times to risk of infection with HIV compared to persons who are not infected with HSV-2 [3]. This may or

may not be due to a biological process as implied, but behavioral and the specific populations are vulnerable to infections with both the viruses. Both HSV-1 and 2 have an envelope of lipid-bilayer encasing them and have a double-stranded DNA (~152 kb) as their genetic material. The 12 glycoproteins in the outer layer participate in the entry of the HSV into the cell. The viral genes are expressed in an orderly fashion with the immediate early (IE) genes expressed first, which encode the proteins for the regulation of the viral replication. This is followed by the expression of the early (E) genes, which encode for the enzymes involved in the replication process. Finally, the expression of the late (L) genes takes place, which encode for the structural proteins of HSV [4]. The completion of the replicative cycle results in the generation of assembled virions which are transported via the endoplasmic reticulum/Golgi cargo transport system to the cell membrane, where the virions are released by acquiring a part of the host's cell membrane. HSV infection leads to pain and suffering, which although not always, may be lethal to the host. HSV-1 mainly causes the stromal keratitis in the eye whereas HSV-2 is responsible for genital lesions [4]. No vaccines against HSV are available for public use, although some are undergoing clinical trials. Therefore, drugs like Acyclovir, Valacyclovir and Famciclovir are the only therapeutic solutions available, which are associated with side-effects and limitations in bioavailability [5]. Thus, more suitable therapeutic agents, in terms of optimal bioavailability and diminished adverse effects, is the need of the hour.

MicroRNAs (miRNAs) on the other hand, are gaining a growing attention from the scientific community as the self-molecules which are the key regulators in infection and disease. These 20–24 nucleotides are non-protein coding RNAs which act post-transcriptionally to regulate the expression of the genes [6]. Since its discovery, miRNAs have found their significance in the diagnostics and therapeutics of diseases such as cancers, diabetes and infections of bacteria and viruses [7–13]. Thus, in this chapter, we have made an attempt to review the facts known about miRNAs are discuss their role in herpesvirus infection with our main focus on HSV infections.
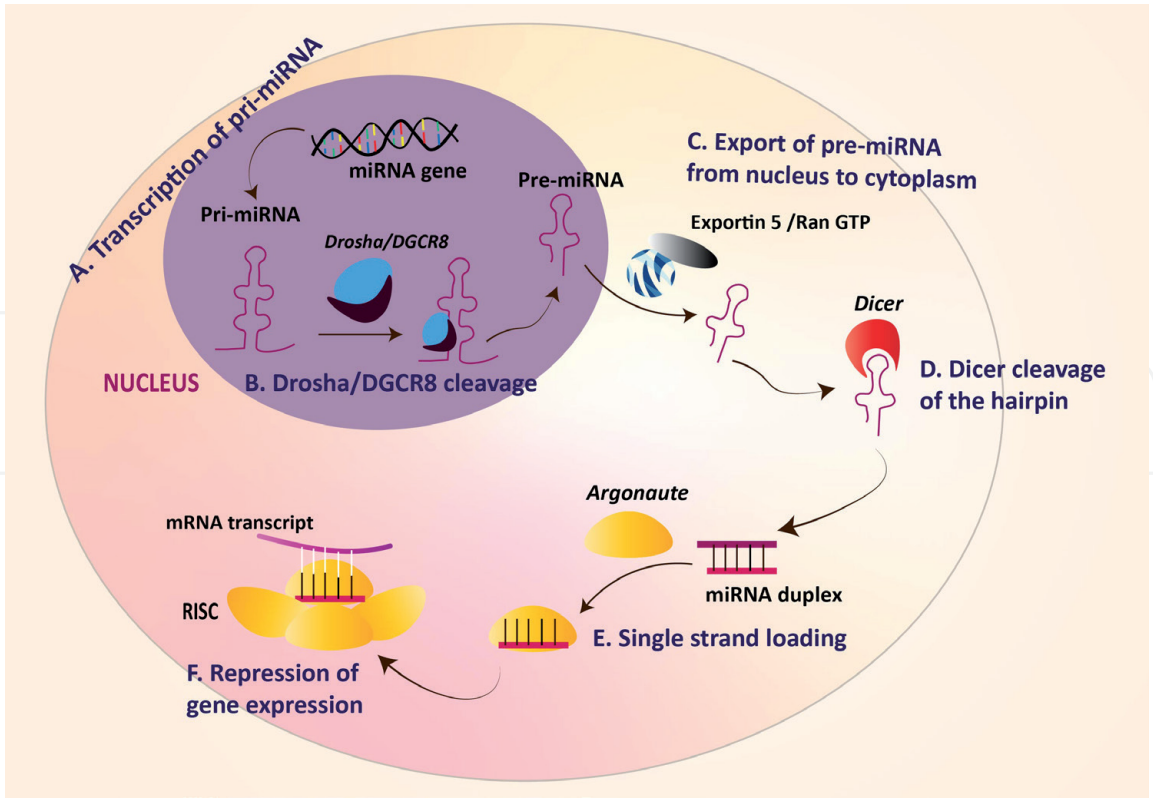
2. Biogenesis of miRNAs

2.1 Canonical pathway for miRNA biosynthesis

The biological synthesis of miRNAs may be either from intragenic or intergenic sequences. Most of the intragenetically synthesized miRNAs are from introns whereas some are from exons of the protein coding genes. miRNAs are also synthesized from intergenic sequences which are independent miRNA genes and have their own, specific promoters. There are canonical as well as non-canonical pathways for miRNA genesis [14]. The canonical pathway for miRNA biogenesis marks the transcription of the primary miRNA (pri-miRNA) from the miRNA genes by RNA Polymerase II (RNA Pol II) in the nucleus. After the transcription the pri-miRNA, which can be as long as 1000 nucleotides in length, they are processed by a microprocessor complex consisting of an RNA-binding protein DGCR8 and an RNase III Drosha. Pri-miRNA methylation by methyltransferase-like 3 (METTL3) marks it for recognition by DGCR8 of the microprocessor complex [15]. DGCR8 recognizes the intersection of the flanking single-stranded (ss) RNA and the stem loop in the pri-miRNA hairpin-structure after which, the Drosha is recruited and involves in a cleavage process [16]. This processing forms the precursor miRNAs or pre-miRNAs (~80 nucleotides in length) having 2 nucleotide 3′ overhangs, which are transported from the nucleus to the cytosol by Expotin-5 (XPO-5)/ Ran-GTP

complex. In the cytosol, the Ran GTPase- activating protein brings about the hydrolysis of GTP, changing the Ran conformation, thereby, releasing the pre-miRNA bound to the XPO5 [17]. After the release, the RNAse III endonuclease Dicer removes ~22 base pairs (bp) of the pre-miRNA terminal loop to form the mature miRNA duplex (**Figure 1**). This processing step of the miRNA allows them to be eligible for loading onto the Argonaute (Ago) complex of proteins which are the essential components of the RNA-induced Silencing Complex (RISC), therefore, the miRNAs mediate their action (**Figure 1**). The decision for the specific loading of a strand of miRNA duplex on the RISC complex is made on the basis of the thermodynamic stability of the two strands and is accompanied by ATP hydrolysis [18]. The strand with a lower 5′ stability or a 5′ Uracil is named as the *guide strand* (~22 nucleotides in length) and is loaded onto the Ago protein, while the strand not loaded onto Ago, named as the *passenger strand*, is cleaved by the slicer activity of the Ago and degraded by the ribonucleases [14, 19].

2.2 Non-canonical pathways for miRNA biosynthesis

While most of the miRNAs are generated via the canonical pathway, there are many which are synthesized by the non-canonical pathways. Although there may be many such non-canonical miRNA synthesis pathways, they use up different combinations of proteins that are participants of the canonical pathway. Primarily, there are two types of the non-canonical pathways, the Drosha/DGCR8 independent route and the Dicer independent route. *Mitrons* are an example of miRNAs synthesized by the Drosha/DGCR8 independent pathway, where the pre-miRNAs
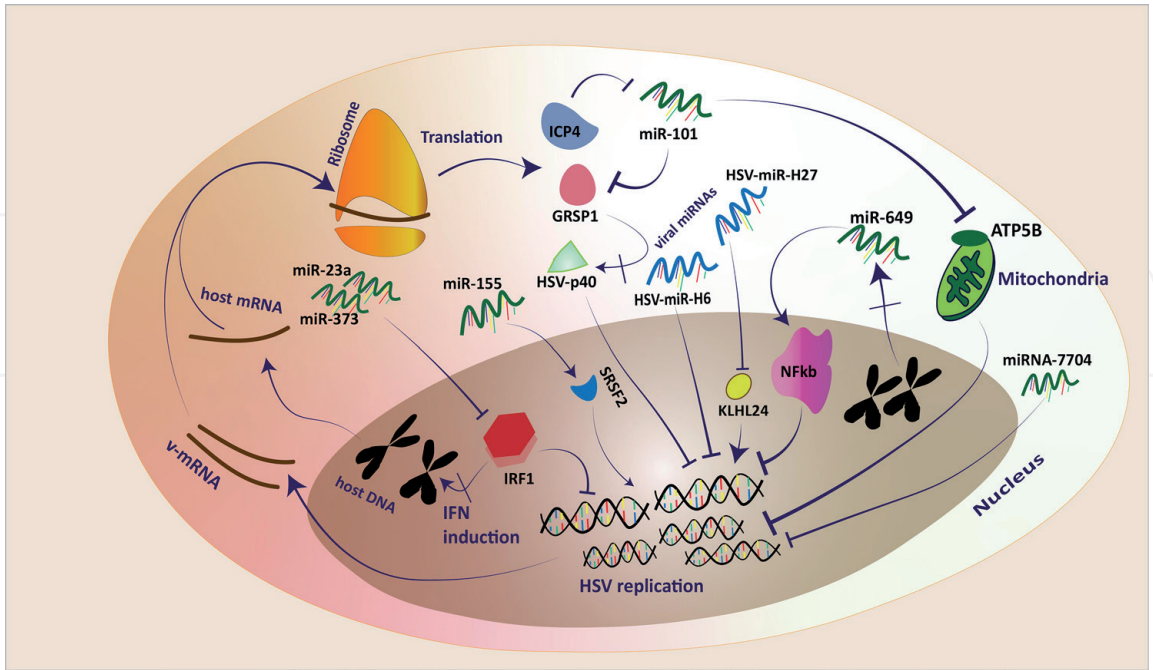

Figure 1.
Biogenesis of miRNAs: A. transcription of pri-miRNA from the miRNA gene by RNA pol II followed by B. Drosha/DGCR8 cleavage of the pri-miRNA to pre-miRNA. C. the pre-miRNA is then exported from the nucleus to the cytoplasm with the help of the Exportin 5 /ran GTP complex where D. dicer cleavage of the hairpin structure takes place. E. One of the strands of the miRNA duplex is loaded onto the RISC, via the ago protein which causes the F. repression of the gene expression by base complementarity-induced mRNA degradation or translation repression.

generated are similar to the Dicer substrates [20]. Here, Exponin-1 needs to transport the miRNA transcripts to the cytosol without Drosha processing it and allows a biased 3p strand loading onto Ago-2. On the other hand, the Dicer-independent pathway involves Drosha processing of the short hairpin RNA (shRNA) transcripts, but is too short to be cleaved by Dicer [21]. Hence, the entire pre-miRNA is loaded onto the Ago-2, which slices the 3p strand. Finally, the trimming from 3′-5′ of the 5p strand concludes the maturation of the miRNA [14, 22].

3. Role of miRNAs in HSV replication

miRNAs play a huge role in the crosstalk between the virus and the host. There are certain viral and cellular miRNAs that regulate the host responses to a viral infection as well as the progression of infection. Both the viral and the cellular miRNAs are capable of regulating the host and the viral mRNAs. Some of the miRNAs that have been identified to be involved during the HSV-1 infection have a direct or indirect impact on the viral replication. These cellular miRNAs may directly target the HSV genome or are manipulated by the HSV through the viral proteome/transcriptome [23]. HSV-1 infected HeLa cells have shown a downregulation of the miR-649 cellular miRNA that targets a ubiquitously expressed cytoplasmic protease, MALT-1, which activates the NF-κB signaling (**Figure 2**). Since NF-κB signaling inhibits HSV-1 replication, the downregulation of miR-649 elevates the expression of MALT-1, increasing the restriction on HSV-1 replication [24]. Similarly, another cellular miRNA which is involved in the suppression of HSV-1 replication is miR-101 (**Figure 2**). The HSV- viral immediate early protein ICP4 directly binds to the promoter of miR-101 to increase the expression of miR-101 in the infected cells thereby decreasing the expression levels of its target GRSP1, which is a scaffolding
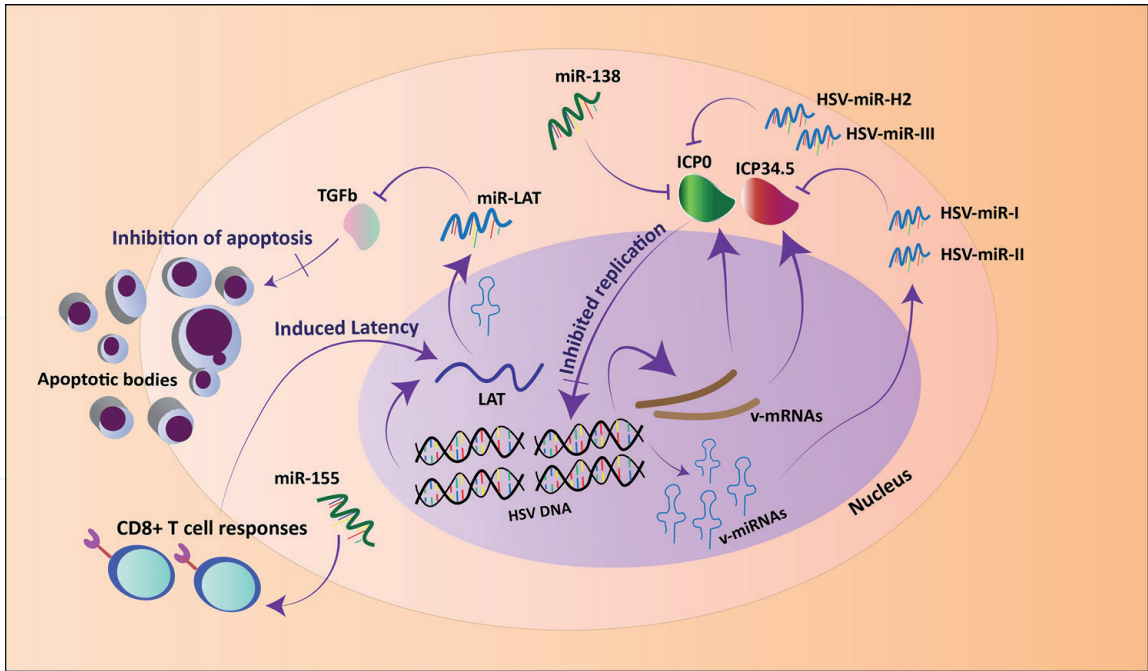

Figure 2.
miRNAs in HSV replication: The figure describes the mode of action of the various cellular miRNAs (green) and the viral miRNAs (blue) that regulate the HSV replication. While the cellular miRNAs, miR-649, −101, −23a, −373 and the viral miRNA, miR-H6 block the HSV replication, the cellular miRNA, miR-155 and the viral miRNA, H-27 promote the HSV viral replication. Both the viral and the cellular miRNAs regulate the host as well as the viral gene expression to modify the replication process either as a host response tying to fight the infection or to establish the infection within the host. Pointed arrowheads indicate progression of an event while blunt arrowheads indicate blockade of an event.

protein that may be involved in the polarization of epithelial cells. GRSP1 directly bind to the HSV-1 p40 and increases the replication of HSV-1. With enhanced suppression of GRSP1, the replication of HSV-1 is hindered. Although it seems surprising that HSV auto-downregulates its replication, it may be a necessary step for the virus to prevent host cell death due to lysis, therefore, maintaining a permissive milieu for virus harboring and replication within the cells [25]. Also, miR-101 can target ATP5B, a subunit of the ATP synthase, to restrict the HSV-1 replication [26]. These studies depict that a single miRNA such as miR-101 could regulate multiple targets to restrict the viral replication. In a study conducted by Shabani et al., a macrophage miR-7704, was capable of reducing the HSV-1 replication in HeLa cells [27]. Another cellular miRNA, miR-23a which targets the Interferon regulatory factor-1 (IRF-1), involved in innate antiviral immunity, is upregulated, so as to escape the host immune responses [28]. Also, a direct suppressor of IRF-1, miR-373, enhances HSV-1 replication by supressing the interferon stimulatory gene responses (**Figure 2**) [29]. Increased expressions of miR-155, a miRNA which could epigenetically increase the transcription of the serine/arginine-rich splicing factor 2 (SRSF2), enhances the HSV-1 replication, due to SRSF2- mediated transcriptional activation of the HSV-1 genes (**Figure 2**) [30]. Some HSV-1 viral miRNAs have also been studied that regulate the virus's replication. HSV-miR-H6, a viral miRNA which is generated profusely during HSV-1 infections, reduces HSV-1 replication by downregulating the viral protein ICP4 (**Figure 2**) [31]. Also, H-27 targets KLHL24 which is a transcriptional repressor (**Figure 2**). Therefore, increase in H-27 expression does not allow KLHL24 to suppress the HSV-1 immediate early and early gene expression, thus, promoting HSV-1 replication [23, 32].

4. miRNAs in acute HSV infection and latency

Encephalitis due to acute HSV-1 or − 2 infection could arise as a direct effect of the HSV invasion of the host or due to the heightened host responses to the virus which causes host damage in the process of virus destruction. Although the incidence of Herpes Simplex Encephalitis (HSE) cases is low, 20% of those affected face neurological after-effects [23]. The inflammation associated with encephalitis often involve the miRNAs, which is also the situation in HSE. miRNAs also contribute to the susceptibility of the cells to HSV infection. This may be the reason for the discovery of a number of cellular miRNAs in HSE. miRNAs miR-155, miR-146a and miR-15b were found to be upregulated in the mouse brain post-HSE [33] and have been associated with neuroinflammation (**Figure 3**) [34]. HSV-1 encoded miR-H28 and miR-H29 were identified to be expressed late during the infection and are exported out of the infected cells in exosomes, thus indicating a role of these miRNAs in viral spread [35]. Also, miR-200 family and miR-182 are the miRNAs identified to be involved in HSE as they target Syndecan-2 (sdc2) which contributes to the biosynthesis of the heparan sulphate required for the attachment and entry of HSV into the cells. Therefore, downregulation of sdc2 by miRNAs is a strategy maneuvered by the host to resist the spread of the virus [33]. This also depicts that mutations in the miRNA sequence or the mRNA target are key players in varied susceptibility to the HSV infection of the central nervous system.

The opposite of excessive HSV pathogenesis is HSV latency, a phase of HSV infection characterized by minimum genome replication. HSV uses neurons as the hideaway for escaping the spotlight for the immune responses while sheltering itself within the host. Since the discovery of HSV- miRNAs in 2006, many miRNAs have been identified to participate in the different stages of viral latency [36] miR-LAT (Latency associated transcript), a miRNA generated from the exon 1 of

Figure 3.
miRNAs in HSV latency: Majorly, the LAT-associated v-miRNAs participate in the induction, establishment and maintenance of latency of the HSV in the cells. HSV-miR-I and miR-II suppress the ICP34.5 expression to restrict HSV replication and promotion of the HSV latency. HSV-miR-H2 and miR-III inhibit the ICP0 expression to suppress the HSV replication. HSV-miR-LAT inhibits apoptosis to allow the infected cell and the virus to survive and establish a latent infection. There are two cellular miRNAs that contribute to the latency. miR-138 promotes latency by preventing ICP0-triggered viral replication whereas miR-155 contribute to the maintenance of latency via the induction of the CD8+ responses.

the HSV1-LAT gene, is responsible for the TGF-β mediated anti-apoptotic effects on the cells during latency. HSV-miR-H2 has been found to suppress the immediate early protein ICP0, therefore, inhibiting the replication to promote HSV latency (**Figure 3**) [37]. On the other hand, HSV2-miR-H6, a miRNA associated with HSV2-LAT, contributes to the reactivation of the virus from latency [38]. Mutation studies on both these miRNAs confirm their effects. miR-I, is another HSV2-LAT associated miRNA which reduces the expression of ICP34.5, a neurovirulence factor, to establish latency in the dorsal root ganglia [39]. A similar study by the same group identified miR-II and miR-III miRNAs from the HSV2-LAT, with miR-II targeting ICP34.5 and miR-III targeting ICP0, to maintain latency (**Figure 3**) [40]. Furthermore, the cellular miRNAs also engage in the events of HSV latency. miR-155 is involved in the maintenance of latency via the elicitation of CD8 responses [41]. Similarly, enhanced expression of miR-138 in the neurons, to target ICP0 for suppression (**Figure 3**), is crucial in maintaining the HSV-1 latency and survival of the hosts [42]. The crosstalk between the viral/cellular miRNAs, amongst themselves, and with the host transcriptome decides for the maintenance of latency which may be for the lifetime, or trigger the reactivation of the virus.

5. Role of miRNAs in the immunological events of HSV infection

Ocular infection by HSV-1 may lead to chronic inflammation resulting in lesions of stromal keratitis (SK). The immunological events underlying the development of SK involve organized T-helper 1 (Th1) and T-helper-17 (Th17) cells, which produce IFN-γ and IL-17, respectively [43, 44]. Also, the involvement of the regulatory T cells (Treg) guides the exacerbation or abatement of the keratitis [45, 46] miRNAs also regulate the development, activation, function and recruitment of the Th and

the Treg cells [47]. A pro-inflammatory miRNA, miR-155 is known to be upregulated during SK and leads to the enhancement of the Th1 and Th17 responses and helps promoting the keratitis. Antagomir nanoparticles containing the anti-miR-155 sequences have been shown to downregulate miR-155 expression and suppress SK [48]. Also, miR-132 was found to be upregulated during SK, which helps in the advancement of angiogenesis via upregulation of the vascular endothelial growth factor (VEGF) by directly targeting a negative regulator of VEGF, a Ras-GTP inhibitor [49]. The Toll-like receptor (TLR) pathway is an integral innate immune response pathway that is altered in almost all infection scenarios. Similarly, the genes associated with the TLR pathway are modulated post-HSV-2 infection by the miRNAs, miR-124, miR-150, miR-342-5p, miR-1245b-5p, miR-1245b-3p, and miR-592 [50]. Speaking of the innate immune responses, type I Interferon (IFN) signal transduction plays a crucial role in curbing viral replication. Thus, for the virus to establish a progressive infection, it must manipulate the host machinery to overcome the IFN combat. So far, in case of HSV-1, miR-221 is manipulated by HSV-1 to suppress the IFN-β production and effector functions [51]. The major innate immune response involved immediately after the HSV infection is the series of events resulting in acute inflammation, which is essential for virus clearance. This also implies that the infiltrates need to be resolved and the cell debris need to be cleared off so as to maintain the immunological homeostasis of the host, preventing a chronic inflammation that could be lethal [52]. Certain pro-resolving mediators (SPMs) function to resolve the acute inflammatory state and may engage a few miRNAs to do so. The binding of Resolvin (RvD1), a SPM, to its receptor upregulates the miRNAs miR-21, miR-146b, miR-219, and downregulates miR-208a [53, 54]. The target mRNA of miR-219 is the transcript of the gene encoding the 5-lipoxygenase enzyme that leads to the decreased production of leukotriene B4 and increased production of the SPMs. miR-146b suppresses the expressions of IL-8 and RANTES, which are the leucocyte-recruiting chemokines at the inflamed regions [54]. miR-146a is also pro-inflammatory in nature and have been shown to trigger the arachidonic acid-mediated, overproduction of IL-1β, to induce an Alzheimer's-like neuropathological condition in the brain. Since it can directly suppress the complement factor H, it is considered as one of the mechanisms of complement evasion by HSV-1 [55]. Another miRNA upregulated as a result of RvD1 binding is miR-21 which contributes to the establishment of an anti-inflammatory milieu by increasing the production of IL-10 when the resolution of inflammation is vital [56, 57]. Contradictorily, miR-208a, which decreases the IL-10 production and enhances the NFκB activation to prolong the inflammatory events, was itself constrained [54]. It has also been noted that miRNAs can function in a cell/tissue-specific manner. miR-4661 is one such miRNA that promotes acute inflammation in the neutrophils, whereas mediates the cessation of the inflammatory responses in the monocytes and the macrophages via the augmented production of SPMs. It also polarizes the macrophages towards the resolution of inflammation [58]. HSV-1 miR-H8 reduces natural killer (NK) cell- dependent killing of the virus-infected cells by the suppression of the glycosylphosphatidylinositol gene expression [59]. HSV-1 viral miR-H28 induces the production of IFN-γ also to restrict the spread of HSV-1 between cells while not affecting the viral replication, so that optimal transmission between individuals take place [60].

## 6. Other herpesviridae viral miRNAs

The herpes simplex virus 1 and 2 discussed mainly in this chapter are also termed as human herpesvirus (HHV)-1 and 2. The other members of the

herpesviridae family of viruses include the Varicella zoster virus (VZV) or HHV-3, the Epstein Barr virus (EBV) or HHV-4, the human cytomegalovirus (HCMV) or HHV-5, the Roseoloviruses HHV-6 and HHV-7, and the Kaposi's sarcoma-associated herpesvirus (KSHV) or HHV-8 [61]. A common characteristic of the herpesviruses is that all the members are capable of establishing latent infections in their hosts and reactivate when the immune system has been compromised. Herpesvirus reactivation brings about changes in the host signaling pathways with the help of alterations in the miRNA expression [62]. VZV is a neurotropic virus that causes chickenpox in humans. Although there are not many reports on VZV v-miRNAs, nearly 20 miRNAs have been predicted from the VZV genome and some of these miRNAs have been shown to be involved in viral replication [63, 64]. EBV, the first human oncovirus reported to encode viral miRNAs and cause various cancers such as nasopharyngeal carcinoma and Burkitt's lymphoma, encodes 44 miRNAs. The EBV miRNAs target the viral as well as the host mRNAs to regulate carcinogenesis and cellular transformation of the EBV-associated cancers [65]. HCMV, which allows extensive replication in the endothelial as well as the epithelial cells and has a large dsDNA genome of 230 bp, encodes 22 miRNAs [66, 67]. KSHV, a gamma herpesvirus and the causative agent of Kaposi's sarcoma, encodes 25 miRNAs. The family also contains HHV-6 and HHV-7, which are the lesser explored members. A single miRNA, miR-U86, encoded by HHV-6A has been reported to target the expression of the U86 gene which is an IE gene of HHV-6A [68]. Therefore, apart from HSV-1 and HSV-2, the other members of the herpesviridae family also encode a number of miRNAs to regulate their infection cycles in the host. Owing to similarities amongst them, investigations pertaining to one will provide insights regarding the other. Here, we discuss some of the miRNA effector functions that are employed during other herpesvirus infections.

6.1 The human cytomegalovirus (HCMV) miRNAs

The HCMV have co-evolved with their hosts and encoding miRNAs that are capable regulators of cell cycle progression, viral gene expression, apoptosis and host immune response evasion (**Figure 4**). In order to maintain the latent infection, the virus attempts to maintain the hematopoietic progenitor cells (HPCs) in the dormant state. EGR-1 (Early growth response gene-1) is critical in maintenance of the HPC quiescence. miR-US22 is a HCMV miRNA that is expressed during the early infection stages or reactivation to restrict the proliferation of the HPCs. It does so by targeting the host transcription factor, EGR-1, so that the HCMV can overtake the host replication machinery for its own replication. Since viral replication is close to negligible during latency, the HCMV miR-US22 is not expressed during this state [69]. Another miRNA mechanism to limit cell proliferation during latency is the suppression of the RhoA, a regulator of the actin dynamics. miR-US25–1 targets the RhoA GTPase to disable mitosis in the cells [66, 67]. The lytic and latent infections are characterized by the abundant expression of the miRNAs, miR-US25–1, miR-UL112-3p, and miR-UL22A. Although most of the HCMV miRNAs are detected during the first 4 hours of infection, miR-UL22A, miR-UL112-3p and miR-UL148D continue to be detected post-IE infection. miR-UL112-3p targets the UL123 viral mRNA that codes for IE72 which is actively involved in viral replication and cell lysis [70] miR-UL148D targets the IE response 5 transcript to indirectly regulate the expression of the viral IE genes through the signaling transduction events induced by Cyclin-dependent kinase 1 (CDK-1) in order to promote latent HCMV infections [71]. The FOXO transcription factors are the facilitators of both mitochondria-dependent and -independent pathways for the induction of apoptosis in cells [72] miR-US5–1 and miR-UL112-3p of HCMV have known to
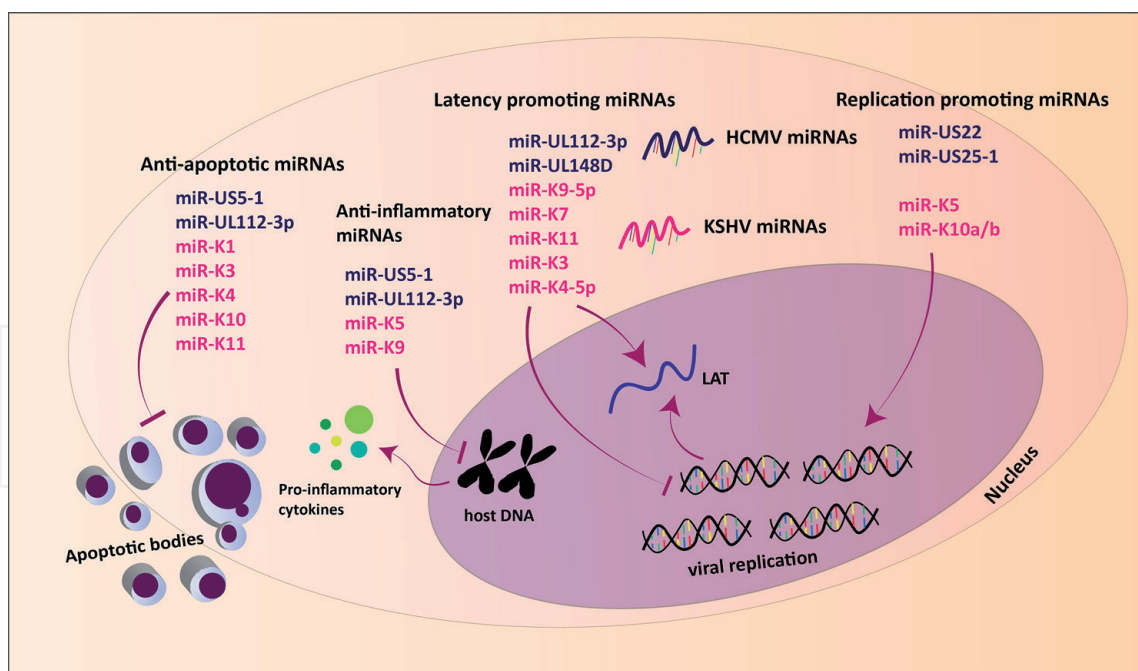
Figure 4.
miRNAs in other herpesvirus infections: The figure summarizes the involvement of the various miRNAs in the different events of other herpesvirus infection. Here, we have taken the example of two herpesviruses, HCMV (navy blue) and KSHV (magenta) to show the extent of v-miRNA involvement during the viral pathogenesis. Mostly, the viral miRNAs involved in replication, latency, cell survival and immune modulation have been mentioned in the figure and are the ones widely explored.

target a member of the FOXO family, FOXO3a [73]. The mechanism involves a downregulation of FOXO3a expression such that its pro-apoptotic functions are limited and binding to the promoter of Bcl-2-like protein 11 (Bim) is restricted. In profusely HCMV replicating cells, the IKK expression was directly constrained by the miR-US5–1 and miR-UL112-3p miRNAs of HCMV, such that production of the pro-inflammatory cytokines, IL-6 and RANTES via the NF-κB pathway was considerably suppressed [74] miR-UL148D directly targets the RANTES transcript to suppress its pro-inflammatory functions [75]. Also, miRUL112-3p directly targets MICB, an MHC I-related chain B, to indirectly repress the NK-cell killing activity so as to protect the infected cells from destruction during the lytic and preferably also during the latent HCMV infections [66, 67, 76].

6.2 Kaposi's sarcoma (KS)- associated herpesvirus (KSHV) miRNAs

KSHV miRNAs regulate the viral mRNAs directly as well as indirectly via the regulation of the cellular mRNAs (**Figure 4**). Certain viral miRNAs participate to establish latency in the KSHV-infected cells. miR-K7 and miR-K9–5p target the KSHV RTA protein, which acts as a switch between the lytic and latency cycles [77, 78]. Also, miR-K11 and miR-K3 function to maintain latency by indirectly suppressing the RTA transcript [79–81]. Another latency-inducing miRNA is the miR-K4-5p which inhibits the retinoblastoma-like protein-2 (RBl2) expression due to which the DNMT1 (methylation enzyme) expression increases. Methylation of the RTA promoter by DNMT1 suppresses RTA expression, inducing latency in the cells [79, 81]. Angiogenesis is an important event in the KSHV infection as it allows the spread of the latency-induced malignancies. GRK2 which regulates the AKT/CXCR2 pathway to establish a reciprocity between viral replication and induction of angiogenesis, is targeted by miR-K3 to decrease viral replication and induce angiogenesis, thus establishing latency [82]. Contradictorily, BCLAF1, Bcl 2-associated factor-1, is the common target for miR-K5, miR-K9 and miR-K10a/b and has been known to

trigger the lytic infection cycle [83] miR-K5 and K9 also suppress the TLR-mediated production of the inflammatory cytokines IL-6, IL-8 and IL-1α by directing interfering with the intermediates, MyD88 and IRAK-1, respectively [84, 85]. The KSHV miRNAs also attempt to inhibit apoptosis and promote cell survival, which is crucial for both malignancy and latency. Therefore, miR-K1, -K3 and -K4 inhibit apoptosis by directly targeting the Caspase-3 protease [86] miR-K10, the viral orthologue of hsa-miR-142-3p, targets TGF-β to promote cell survival and cellular transformation [87, 88] miR-K10a is also the negative regulator of the TWEAK receptor, which is the receptor for the TNF-like weak inducer of apoptosis, thereby, inhibiting apoptosis as well as downregulating the production of IL-8 and MCP-1 to contribute to the KS progression [89] miR-K1 also promotes cell cycle progression by inhibiting p21 [90]. Another target for miR-K1, IκBα, which usually retains NF-κB in the cytoplasm by blocking the nuclear localization signals, is constrained to promote latency and survival of the transformed cells [91]. Activation of NF-κB also inhibits the Warburg effect leading to the declined expressions of GLUT-1 and GLUT-3, suggesting the significance of the metabolic regulation for the proliferation of the KS cells [92]. Just as miR-155 have been considered as the regulatory epicenter of various cancers and viral infections, the KSHV miRNA, miR-K11 mimics some of the functions of this cellular miRNA. miR-K11 blocks the C/EBPβ resulting in the enhanced, IL-6-mediated proliferation of the B cells [93]. It also targets JARID2 leading to increased B cell transformation [94]. Moreover, miR-K11 also inhibits the IFN type I signaling by directly targeting IKKε mRNA [95, 96]. Thus, the generation of cellular miRNA orthologues by the herpesviruses is clearly evident of its co-evolution with its host, such that it diverts the cellular machinery towards its own viral processes while hiding itself efficiently from the host responses.

7. miRNAs as potential biomarkers in herpesvirus infections

With as many miRNAs that are expressed during each of the herpesvirus infections, the recognition of certain miRNAs are biomarkers for these infections is promising. There are a number of reasons that back the concept of miRNA biomarkers in human infections. The distinct pathophysiological events occurring during the infection is reflected in the miRNA expression patterns. For example, where miR-649 is considerably downregulated in HSV-1 infected cells as compared to the uninfected cells to mark the overwhelming participation of NF-κB is fighting the infection, there are certain miRNAs exclusively generated by the HSV (miR-H6, -H27 etc.). miRNAs are also the biomarkers of the HSV infection status within the host as certain miRNAs are specific to the lytic phase (miR-H1) whereas some are specifically expressed during the latency phase (miR-H2–6). miRNAs are easily available for detection in the body fluids such as blood, serum and human dental pulps [97, 98] and so are the v-miRNAs of the *herpesviridae* family members [99]. Although there are a few ongoing clinical studies on miRNAs biomarkers in cancer, the reports on EBV-related cancer miRNAs also being detected in the blood and urine, will boost the EBV research in the same direction [100]. Furthermore, the molecular techniques used for the miRNA detection, such as, the real-time PCR array, microarray profiling and the next-generation sequencing techniques are popular and well established in case of herpesvirus infections as well [101–104]. One of the greatest advantages of using miRNAs as biomarkers is their sustained expressions *in vivo* as compared to the mRNAs. This is because of the presence of exosomes which enclose the miRNAs. Moreover, the miRNAs released extracellularly are bound to the Ago proteins. These mechanisms protect the miRNAs against degradation by the nucleases [35, 105, 106]. Whether v-miRNAs or cellular

miRNAs are better biomarker candidates might be debatable. However, an important consideration in this context is that v-miRNAs are virus-specific whereas host miRNAs are not exclusive for a virus infection. For example, miR-155, which is crucial in HSV-1 latency is also involved in pro-inflammatory functions in other diseases such as cancer, asthma, arthritis, Cystic fibrosis and also recently reported in other viral infections, such as that of the Sars-CoV-2 [41, 107, 108]. Therefore, a panel of host and viral miRNA combinations may serve as an appropriate biomarker in case of each of the herpesvirus infection.

8. Therapeutic considerations of miRNAs in herpesvirus infection

miRNAs can also be referred to as the endogenous post-transcriptional gene regulators and have a special advantage over drugs. miRNAs are self-molecules and hence are safer than any of the synthetic or natural compounds used as therapeutics against the infections. Another feature of miRNAs that make them interesting candidates for therapeutic considerations is their ability to regulate more that one gene expression, and inversely, the expression of a single gene can be modulated by more than one miRNA. Being the regulators of gene expression, modification of the miRNAs is an approach for changing the course of an infection or a disease. There are two ways by which the miRNA expression may be modified. One of modifications include reintroduction of the miRNA expressions by the use of specific miRNA mimics, while the second is to block the infection-induced/ modified miRNA expression by the use of the specific-miRNA inhibitors [23]. The use of miRNA mimics and inhibitors have been trending in the field of research on infectious diseases since the successful progression of miRavisen through the clinical trials to be established as therapeutics against the Hepatitis C virus [109] miRavisen is a miRNA inhibitor of miR-122, a miRNA which increases the HCV viral replication [110, 111]. Similarly, inhibitors of miR-373 or HSV-miR-H27 can be administered as therapeutics to decrease the HSV viral load in the hosts. There have also been studies where mimics of miRNAs have proved to be useful in restricting viral replication. Recently, a study identifying the significance of miR-29b mimics have been reported to decrease the Rotavirus infection considerably [112]. Likewise, mimics of miR-7704 and miR-101 could be encouraged in the HSV therapeutic research. Furthermore, the reported miRNA research could be compiled to develop therapeutic formulations involving combinations of mimics and inhibitors to synergistically suppress the HSV infection in the host. However, miRNAs, like any other therapeutics, face the challenges of target-specific delivery and off-target effects. These challenges are also being addressed by the researchers with the synthesis of appropriate miRNA-loaded nanoparticles which ensures on-site targeted delivery and optimal bioavailability while maximally reducing the off-target effects [6]. All-in-all, the potentiality of miRNAs as therapeutic agents against viral infections is being explored explicitly, also implying that their clinical applications in herpesvirus infections is inevitable.

9. Conclusion

Elucidation of miRNAs have emerged as a promising field of research due to the capability of the miRNAs to be easily manipulated to alleviate an infection. The fact that a single miRNA can target more than one gene expression (viral, cellular, or both) to suppress the viral infection is equally fascinating and efficient. The significance of miRNAs as biomarkers and therapeutic agents in infection makes

them acceptable to the researchers. All the more, the commercially available mimics and inhibitors of the miRNAs makes the research pertaining to them affordable. However, miRNAs face the challenges of specific, on-site delivery, long-term miRNA stability and off-target consequences, and yet, have been FDA-approved under the small molecule therapeutics category. The challenges of targeted delivery and optimum bioavailability is met with the miRNA-loaded nanoparticles, which diminish the off-target effects as well. Thus, with miRNAs finding their utility into a variety of applications, expansion of the miRNA investigations, both in basic and applied research, is evident.

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