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The Role of Human Herpesvirus-Encoded MicroRNA in Host Virus Interaction

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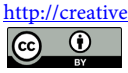

Abstract

Human Herpesviruses (HHVs) are a group of large DNA viruses that can establish lifelong infections in their hosts. They achieve this by switching between two phases: the lytic phase, where the virus actively replicates, and the latent phase, where the virus remains dormant but can reactivate later. A key factor in this process is microRNAs (miRNAs)—small, non-coding RNA molecules that regulate gene expression. In human cells, miRNAs play a crucial role in controlling various biological processes, and their disruption has been linked to diseases like cancer. Interestingly, herpesviruses have evolved ways to manipulate the host's miRNA system to their advantage. By interfering with these regulatory pathways, the virus can evade immune detection, prevent cell death (apoptosis), and promote either viral persistence or active replication, depending on what benefits its survival. This review explores the role of viral microRNAs (v-miRNAs) in human herpesvirus infections, focusing on how they influence the virus's lifecycle and contribute to disease. HHVs are unique in that because many of them encode their own v-miRNAs, which help them hijack the host's cellular machinery. A key aspect of this interaction is how these viral miRNAs suppress immune responses, affecting both innate and adaptive immunity. Additionally, research has shown that herpesviruses can package their miRNAs into exosomes-tiny vesicles that can transfer viral messages between cells, altering the function of recipient cells and promoting infection. This paper specifically examines the functions of HHV-derived v-miRNAs in host-virus interactions, with a focus on how they help the virus persist in the body. Among the eight known human herpesviruses, v-miRNAs have been identified in Herpes Simplex Virus 1 & 2 (HSV-1 & HSV-2), Human Cytomegalovirus (HCMV), Human Herpesvirus-6B (HHV-6B), Epstein-Barr Virus (EBV), and Kaposi Sarcoma-Associated Herpesvirus (KSHV). Understanding how these viral miRNAs function could provide deeper insights into herpesvirus pathogenesis and potential therapeutic strategies.

Subject Areas

Immunology

Keywords

Human Herpesvirus, Viral-miRNAs, Host-Virus Interaction, Infection, Immunity

1. Introduction

Human Herpesviruses (HHV) are large, double stranded coated DNA viruses encoded by an icosapentahedral capsid [1]. The capsid is surrounded by amorphous protein called tegument [2]. There are more than 100 known herpesviruses, only 8 routinely infect humans: Herpes Simplex virus types 1 and 2, Varicella-Zoster virus, Cytomegalovirus, Epstein-Barr virus, Human Herpesvirus 6 (variants A & B), Human Herpesvirus 7 and Kaposi's Sarcoma virus (HHV8) other than that, a similar virus, called B-virus occasionally infects humans [3]. HHV genomes are large (approximately 120 - 180 kb) that/which encode a large repertoire of protein-coding genes to overcome numerous host lifeline and cellular functions. Herpesvirus encoded v-miRs was first discovered by Pfeffer *et al.* [4] which showed that these viruses have evolved with another critical regulatory RNA called miR. HHV's miRNAs can target both cellular and viral mRNAs. Host miRNA targeted mRNAs are mostly related to cell proliferation, regulation, apoptosis, and host immunity [5]. Most of the HHV are reported to encode many (22 - 44) v-miRs, indicating unique requirement of these non-coding RNAs in HHV-host interaction. Like host miR, v-miR can interact with the 3'untranslated region (UTR) of the target mRNA to regulate gene expression. This interaction results in translation inhibition and/or destabilization of cognate transcripts including host-and virus-encoded [6].

1.1. Classification of HHV

Human Herpesviruses are divided into three groups based on replicative cycle and host range [7] (**Figure 1**).

- Alpha herpesvirus: Herpes simplex virus 1 & 2 and Varicella zoster virus are the members of alpha herpesvirus [8] (Short replicative cycle and have a broad host range, induce cytopathology in monolayer cell cultures).
- Beta herpesvirus: Cytomegalovirus, Human herpesvirus 6 (A & B) and 7 are the members of beta herpesvirus [8] (Long replicative cycle and restricted host range).
- Gamma herpesvirus: Epstein-Barr virus and Kaposi's Sarcoma virus (HHV8) which may lead to carcinogenesis are the members of gamma herpesvirus [9] (Restricted host range).

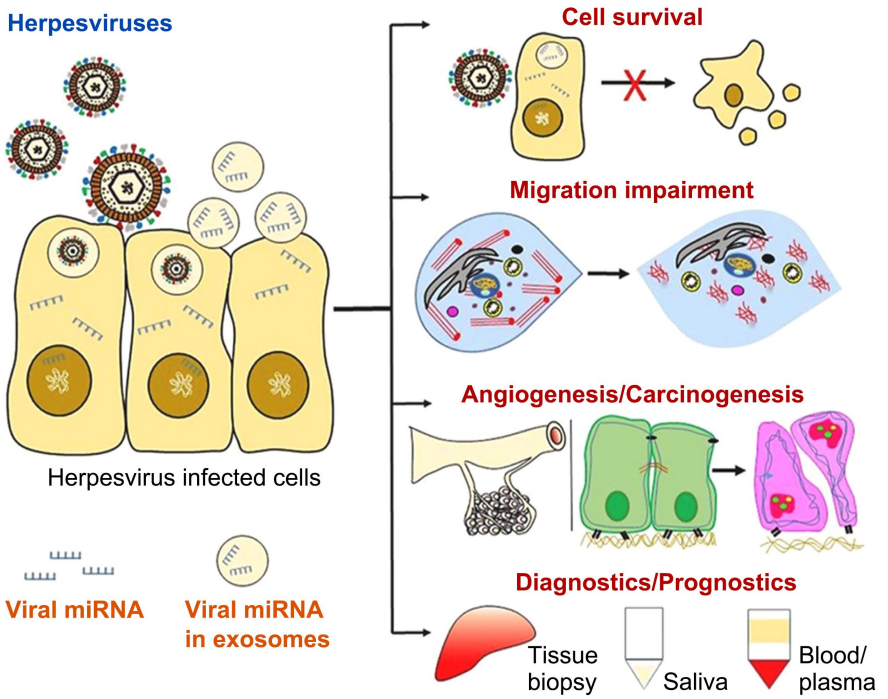

Figure 1. Human Herpesvirus encoded microRNAs in host-viral interaction showing herpesvirus infected cells, migration impairment, angiogenesis/Carcinogenesis, Diagnostics/Prognostics and their transmission through blood plasma, saliva and tissue biopsy.

1.1.1. Alpha Herpesvirus

Alpha herpesviruses are large DNA viruses and represent the largest subfamily of the Herpesviridae family. This group includes viruses that infect both humans and animals, such as herpes simplex virus (HSV), varicella-zoster virus (VZV), pseudorabies virus (PRV), and bovine herpesvirus 1 (BoHV-1), among others. A key feature of these viruses is their diverse envelope proteins, which are integrated into various cellular membranes, including those of the endoplasmic reticulum (ER), Golgi apparatus, and plasma membrane during infection. Notably, the cytoplasmic domains of several alpha herpesvirus envelope proteins contain specific tyrosine-based amino acid sequences. Recent studies suggest that these motifs play crucial roles in the viral life cycle. They have been implicated in processes such as endocytosis, intracellular trafficking, targeted transport to basolateral and axonal regions, and signal transduction. These functions are essential for efficient viral replication, spread, and host cell interactions [10].

1.1.2. Beta Herpesvirus

The beta herpesvirus subfamily includes four human-infecting viruses: human cytomegalovirus (HCMV) and human herpesviruses 6A, 6B, and 7. Like all herpesviruses, beta herpesviruses have a well-structured virion consisting of four main components: the genome, capsid, tegument, and envelope. Their genetic material is double-stranded DNA (dsDNA), with genome sizes ranging from approximately 145 to 240 kb. The capsid, a geometric shell, securely holds a single copy of the viral genome. Surrounding the capsid is the tegument, a dense layer packed with

proteins and RNA molecules that become active as soon as the virus enters a host cell, aiding in early infection. The outermost layer, the envelope, is a lipid bilayer embedded with viral glycoproteins, which help protect the virus during transmission and enable it to infect new cells [11].

1.1.3. Gamma Herpesvirus

Gamma herpesviruses are classified into two main groups: Lymphocryptovirus, which includes Epstein-Barr virus (EBV or HHV-4), and Rhadinovirus, which includes Kaposi's sarcoma-associated herpesvirus (KSHV or HHV-8). Research suggests that primate rhadinoviruses can be further divided into three groups: KSHV-like viruses, a separate but closely related group found in Old World primates (such as rhesus rhadinovirus, RRV), and New World monkey rhadinoviruses, represented by herpesvirus saimiri (HVS). All gamma herpesviruses have a similar genomic structure, with the 172-kilobase (kb) linear double-stranded DNA genome of the EBV B95-8 strain serving as a reference, as it was the first gamma herpesvirus to be sequenced. These viruses also share certain features with alpha and beta herpesviruses, especially in how they replicate. During lytic replication, the viral genome is packaged into a protein shell (capsid), then surrounded by a lipid envelope before being released from the host cell [12] (See **Table 1**).

Table 1. Common clinical manifestation of different Human Herpesvirus, Pathogenesis, Host Defense and Epidemiology.

Types of HHV	Clinical manifestation	Pathogenesis	Host defense	Epidemiology
Human Simplex virus (HSV-1 & 2)	Gingivostomatitis, herpetic keratitis, dermal whitlows, encephalitis & Genital herpes [13].	Replicates initially in epithelial cells, producing a characteristic vesicle on an erythematous base. After that it ascends sensory nerves to dorsal root ganglia where after an initial period of replication, it established latency [14].	Interferon and humoral, mucosal, and cellular immunity are important defenses [15].	HSV-1 transmission is primarily oral and HSV-2 primarily genital. Transmission requires intimate contact [16].
Varicella-Zoster virus (VZV)	VZV infection causes varicella(chickenpox). Reactivation of latent virus causes herpes zoster (shigles).	Usually transmitted by droplets and replicates initially in the nasopharynx. Latency is established in dorsal root ganglia.	Interferon, humoral, mucosal, and cellular are important defenses.	VZV is highly contagious: about 95% of adults show serologic evidence of infection. [17]
Human Cytomegalovirus (HCMV)	Mononucleosis syndrome, systemic disease observed in congenital infection or immunocompromised individuals.	It replicates mainly in the salivary glands and kidneys and is shed in saliva and urine. Replication is slow, and the virus induces characteristics giant cells with intracellular inclusion.	-	Transmission is via intimate contact with infected secretions. Cytomegalovirus infections are among the most prevalent viral infection worldwide. [18]

Continued

Epstein-Barr virus (EBV)	Infectious mononucleosis, oral hairy leukoplakia, lymphoproliferative syndrome in immunocompromised hosts.	EBV replicates the epithelial cells of the oropharynx and in β-lymphocytes.	NK and NKT cells likely contribute to initial control of EBV infection in humans. Adaptive immunity is fundamental for protection against EBV.	EBV is transmitted by intimate contact particularly via the exchange of saliva. [19]
HHV6 (A & B) and 7	Human herpes viruses 6 and 7 are associated with exanthem subitem (roseola) and with rejection of transplanted kidneys.	The primary target cell for HHV-6 is CD4+ T lymphocytes, a characteristic that it shares with HIV. HHV-7 has been associated with febrile seizures and has been implicated as a possible cause of encephalitis.	-	Antibodies to this virus are present in almost everyone by age 5. [20]
Kaposi's Sarcoma virus (HHV8)	Kaposi's Sarcoma, Primary effusion lymphomas and Castleman's disease [21].	Pathogenesis is poorly understood.	-	HHV-8 transmited to uninfected partners through behaviors associated with exposure to saliva or genital secretions.
B-virus	B virus infection is extremely rare. However, it can lead to severe brain damage or death if you do not get treatment immediately [22].	B-virus is transmitted to humans by the bite of infected rhesus monkeys and is transported up neurons to the brain.	-	The reservoir for the disease is latent infection in rhesus monkeys particularly from South Asia and India.

2. Virus-Encoded microRNAs (V-miRNAs)

The first v-miRs were discovered in 2004 in human B-cells that were latently infected with γ-herpesvirus EBV. V-microRNAs are tiny, multifunctional, non-protein coding RNAs that are tightly clustered within a few viral transcripts [23]. More than 250 different miR of viral origin have been identified till date and the list continues to expand. Both host and viral miR are involved in viral tropism, pathogenesis, and latency [24]. While host miR can function as antiviral defense, viruses encode suppressors (RNA protein) to contract miR functions and have evolved mechanisms to utilize host miR for their benefit [25]. Molecular mechanisms of v-miRNAs

2.1. Functions of v-miRs in Different Types of HHV

- Alpha Herpesvirus: → Herpes Simplex virus 1
  → Herpes Simplex virus 2

HSV-1: 27 miR in HSV-1 have been documented till now and over half of the

miR are generated from latency associated transcript (LAT) locus, while others are expressed during productive infection from other regions of the viral genome. LAT-encoded miR may repress transcripts that are essential for lytic gene expression and work to establish or maintain latency [26].

- Beta Herpesvirus: → Human Cytomegalovirus; → Huan Herpesvirus 6B

While other miR genes are found in viral genome, they are most associated with the lytic stage of the viral lifecycle [27].

- Gamma Herpesvirus: → Epstein-Barr virus; → Kaposi's Sarcoma Herpesvirus

They both encode large repertoire of miR. V-miRs may play a role in viral transformation of B-cells, as multiple mRNA targets have been documented [28].

2.2. Molecular Mechanism of Viral miRNAs in Herpesvirus-Host Interaction and Pathogenesis

Herpesvirus-encoded microRNAs (v-miRNAs) play a crucial role in modulating host cellular processes to promote viral persistence, immune evasion, and pathogenesis. These v-miRNAs function by targeting both host and viral mRNAs, leading to post-transcriptional regulation that affects viral latency, immune suppression, and oncogenesis.

Regulation of Viral Latency and Reactivation

- v-miRNAs suppress viral immediate-early (IE) gene expression, preventing activation of lytic replication. For example, EBV miR-BARTs and KSHV miR-K12-1 repress viral trans activators, maintaining a latent infection state.
- Latency-associated transcript (LAT)-encoded miRNAs in HSV-1 inhibit pro-apoptotic genes, helping the virus persist in sensory neurons.

Immune Evasion and Host Immune Modulation

- v-miRNAs downregulate innate immune signaling pathways, particularly by targeting key molecules in Toll-like receptor (TLR), RIG-I-like receptor (RLR), and cytokine signaling pathways.
- HCMV miR-UL112-3p suppresses TLR2 expression, inhibiting the pro-inflammatory response and reducing immune recognition.
- KSHV miR-K12-11 mimics host miR-155, altering B-cell signaling and promoting immune evasion.

Inhibition of Apoptosis and Promotion of Cell Survival

- Herpesvirus v-miRNAs target host pro-apoptotic genes to promote cell survival, ensuring long-term viral persistence.
- EBV miR-BHRF1-2 suppresses p53 and BIM, preventing apoptosis in infected B cells.
- HSV-1 miR-H6 inhibits SMAD3, interfering with TGF-β signaling and apoptosis induction.

Oncogenesis and Cellular Transformation

- Certain herpesviruses, such as EBV and KSHV, encode miRNAs that drive oncogenic transformation by targeting tumor suppressors and modulating cell cycle regulators.
- EBV miR-BART5 inhibits PUMA, a key pro-apoptotic factor, promoting the survival of EBV-infected epithelial cells and contributing to nasopharyngeal carcinoma.
- KSHV miR-K12-6-3p downregulates TP53INP1, reducing p53-mediated apoptosis and facilitating viral tumorigenesis.

Modulation of Host Transcriptome via Exosomes

- v-miRNAs are packaged into exosomes and secreted into the extracellular environment, influencing uninfected neighboring cells.
- EBV-derived miR-BART15 targets NLRP3, suppressing inflammasome activation and dampening host immune responses.
- HCMV and KSHV exosome miRNAs can modulate the tumor microenvironment, contributing to angiogenesis and immune suppression.

By interfering with host gene expression, v-miRNAs facilitate herpesvirus latency, immune evasion, and oncogenesis, ensuring long-term persistence and pathogenesis. Understanding these regulatory mechanisms could provide novel therapeutic targets for antiviral interventions and immunomodulatory strategies.

3. The Role of Viral-miRs in Host Immune Response and Virus Immune Evasion

INNATE IMMUNITY

When a person gets infected with Human Herpesvirus (HHV), the body's first line of defense is the innate immune response. This system detects viral antigens and quickly reacts to limit the infection. It also helps trigger the adaptive immune system, which includes antibody production and specialized immune cells that provide long-term immunity. However, HHV is exceptionally skilled at evading the immune system. It not only infects the host but also manages to replicate, establish latency, and reactivate when conditions are favorable. For the virus to complete its lifecycle, it must weaken the body's innate immune response; otherwise, a strong adaptive immune reaction would eliminate it. One-way HHV achieves this is through viral microRNAs (v-miRs). These small RNA molecules interfere with the host's immune defenses by suppressing specific genes involved in the antiviral response. Normally, host cells recognize invading viruses through pattern recognition receptors (PRRs), which act like security sensors. When these sensors detect a virus, they trigger an immune reaction to stop the infection. However, HHV uses v-miRs to disrupt this process, allowing the virus to persist in the body. This ability to manipulate the immune system is what makes HHV so successful at establishing long-term infections. PRRs are generally categorized into 7 distinct families including:

- TLRs (Toll-Like Receptors)
- RLR (Retinoid acid-inducible gene-I-Like Receptors)

- NLR (Nucleotide oligomerization domain-Like Receptors)
- CLRs (C-type Lectin Receptors)
- AIM2-Like Receptors
- CGAs (Cyclic cGMP-AMP synthase)

3.1. Pathogen Recognition Receptors: (PRRs)—The Body's First Line of Defense

Our immune system has a remarkable ability to detect and respond to harmful invaders like bacteria, viruses, and fungi. One of the keyways it does this is through Pathogen Recognition Receptors (PRRs)-special proteins that help identify these threats and trigger an immune response. Over millions of years, both pathogens (like viruses and bacteria) and their hosts (humans and animals) have evolved alongside each other. To defend itself, the host has developed mechanisms to differentiate between self (its own cells) and non-self (invading pathogens). This distinction is crucial in preventing infections while avoiding damage to the body's own tissues. PRRs are found in different parts of the cell.

- On the cell surface—to detect external pathogens.
- Inside endosomal membranes—to recognize pathogens that have been engulfed by the cell.
- Within the cytoplasm—to identify intracellular threats.

These receptors identify unique molecular patterns present in pathogens, known as Pathogen-Associated Molecular Patterns (PAMPs) [29] [30]. Based on the specific molecular motifs they recognize, PRRs are classified into three major categories:

- Toll-like receptors
- NOD-like receptors
- RIG-I like receptors

3.1.1. Toll-Like Receptors

TLRs are present on cell and endosomal surface and play a key role in innate immune activation. In general, extracellular pathogens are recognized by surface TLRs, while intracellular pathogens and their ligands are recognized by endosomal TLRs. HHV has mechanisms to thwart immune responses. HHV utilizes v-miRs as an important tool to suppress innate immunity [31] [32]. Among the TLRs, TLR2 in conjunction with TLR1 or TLR6 is a key receptor in recognizing HCMV, EBV, HSV-1/2, and HSV-derived ligands [33]. HCMV encoded miR-U-112-3p targets TLR2 to inhibit the proinflammatory responses by HCMV ligand [34]. MYD88 (Myeloid differentiation primary-response gene 88) and IRAK1 (Interleukin-1 receptor-associated kinase) are two key components of TLR signaling. KSHV encoded miR-k12-5 targets MYD88 to suppress the TLR-mediated activation of cytokine production. KSHV encoded miR-k12-9 targets IRAK1 to suppress the TLR-mediated activation of cytokine production [35]. Activation of NFκB is mediated by two IκB kinase namely IKKα and IKKβ. Two HCMV miR: miR-US5-1 and miR-UL112-3p suppress IKKα and IKKβ levels to limit NFκB activation.

KSHV encoded miR-K12-11 targets IKKε (which is involved in KSHV reactivation) to suppress antiviral pathway and promotes latency maintenance [36]. Similarly, KSHV miR-K12-3 and miR-K12-7 targets an important transcriptional regulator C/EBVβ that suppress IL-6 and IL-10 cytokines and promotes virus reactivation [37].

3.1.2. NOD-Like Receptors and RIG-1 Like Receptors

NLR and RLR are a family of multiple cytosolic helicases that detect invading pathogens or host-derived damage signals in the cytosol and trigger innate immune response primarily by NFκB and MAPK signaling cascade. A key feature of NLR proteins is that they oligomerize to form large complexes called inflammasomes. EBV encoded miR-BART-15 targets NOD-like receptors (NLR) to suppress inflammasome formation and hence IL-1p/IL-18/ROS production [38]. Similarly, EBV miR-BART16 targets CREBBP (CREB-binding protein) to inhibits type I interferon signaling [39].

3.1.3. Cytokine Receptors: Cytokine Receptors and Viral miRNAs

Cytokines play a key role in the immune system by signaling to nearby cells (paracrine signaling) or the same cell (autocrine signaling) to help fight infections. Two important proinflammatory cytokines, IL-1, and IL-6, are produced early during herpesvirus (HHV) infections, helping the body mount an immune response [40]. However, herpesviruses have evolved ways to block cytokine signaling to avoid detection and persist in the body. The examples of HHV blocking Cytokine Signaling are given below:

1) Epstein-Barr Virus (EBV):

- miR-BHRF-1-2-5p targets IL-1R1, reducing IL-1 signaling and weakening the immune response.
- miR-BART-6-3p suppresses IL-6R, impairing IL-6 signaling, which is crucial for immune activation and T cell growth [41].

2) Human Cytomegalovirus (HCMV):

- miR-UL148D targets ACVR1B, a key component in the activin pathway, reducing IL-1 and IL-6 production in monocytes.
- miR-UL112-1 inhibits IL-32, which normally triggers inflammatory cytokines like IL-1β, IL-6, IL-8, and TNF-α [42].

3) Herpes Simplex Virus 2 (HSV-2):

- miR-H9-5p suppresses SOCS2, a protein involved in immune regulation and natural killer (NK) cell function [43].

4) Kaposi's Sarcoma-Associated Herpesvirus (KSHV):

- miR-K10 targets TWEAKR, blocking the receptor for the inflammatory cytokine TWEAK, reducing inflammation.
- miR-K6 and miR-K9 interfere with the NF-κB signaling pathway, lowering the production of inflammatory cytokines [44].

By suppressing these cytokine receptors and pathways, HHVs weaken the immune response, creating a more favorable environment for infection. This not only

prevents antiviral defenses but also helps infected cells survive longer, allowing the virus to persist in the body (Figure 2).

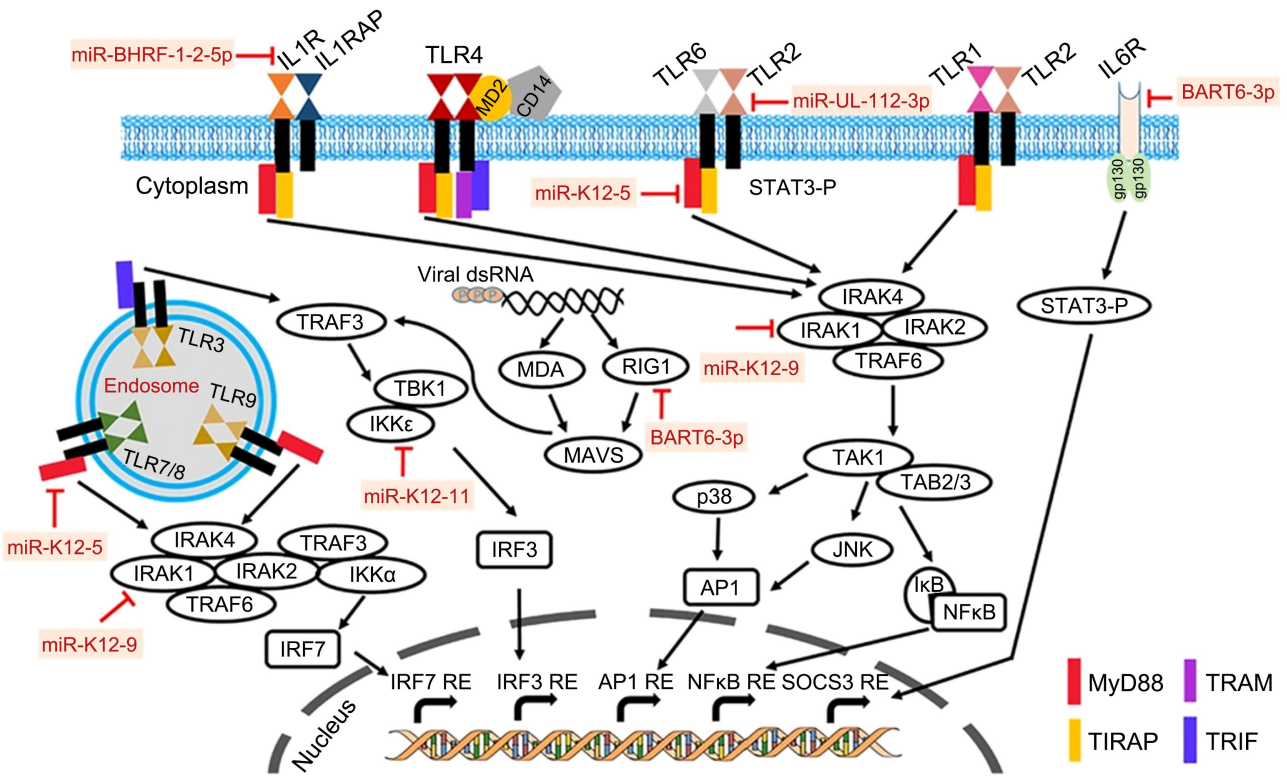

Figure 2. Illustrates how herpesvirus-encoded microRNAs (v-miRs) interfere with key innate immune signaling pathways to evade the host immune response. It highlights: Suppression of Toll-like receptors (TLRs) (e.g., TLR4, TLR6, TLR7/8) and IL-1R/IL-6R signaling by v-miRs like miR-BHRF-1-2-5p, BART6-3p, miR-K12-5, and miR-UL-112-3p.Disruption of key immune regulators (e.g., TRAF6, TBK1, MAVS, IRF3, and NF-κB) by v-miRs like miR-K12-9, miR-K12-11, weakening antiviral responses. Blocking of proinflammatory cytokine production through interference with p38, AP1, and NF-κB pathways, helping herpesviruses persist in the host. The above figure emphasizes how herpesviruses hijack immune pathways using v-miRs to suppress inflammation, evade immune detection, and ensure long-term infection.

ADAPTIVE IMMUNE RESPONSE

The adaptive immune system plays a crucial role in fighting infections by recognizing and remembering foreign invaders. This response begins when dendritic cells and macrophages-key players in the innate immune system, activate lymphocytes. However, this process takes time, often days to weeks, to fully develop. Once activated, the adaptive immune system creates immune memory, allowing the body to respond more quickly if the same virus attacks again. In healthy individuals, this helps keep herpesviruses under control. But in

immunocompromised individuals, where the immune system is weaker, herpesvirus infections are more common and can cause severe disease. To survive and spread, herpesviruses must block the activation of adaptive immunity. The way they do this is through viral microRNAs (v-miRs), which help the virus evade detection. The following section explores how v-miRs interfere with the adaptive immune response.

3.2. Antigen Processing and Presentation

There are two distinct antigen processing and presentation pathways. In general, major histocompatibility complex (MHC-I) and MHC-II process intracellular and extracellular antigens respectively [45]. MHC-II presentation to CD4+T cells results in polarized cells with specific antiviral immunity [46]. Several HHV-encoded proteins inhibit both pathways. Multiple HHV-encoded proteins target the generation of peptides (including viral antigens) by blocking the activity of host proteins required in the process. HHV proteins have been shown to interfere with proteosome activity, transport of viral peptide to MHC-I to cytosolic degradation, and redirecting surface bound MHC-I peptide complex to lysosome for degradation. The role of v-miRs in interfering antigen processing/presentation pathways is reported. An increasing number of HHV-encoded v-miRs, are demonstrated to specifically target genes that participate in antigen presentation and activation of T-cell as well as NK cells. Different HHV encode miR that target the same gene, while multiple v-miRs from the same HHV exhibit sequence complementarily for a single gene.

3.3. T-Cell Activation and Polarization

Antigen-presenting cells (APCs) display viral epitopes that are recognized by T-cells leading to their activation. This is mediated by a set of stimulatory and costimulatory molecules present on APC and T-cells. To survive inside the host, it is imperative for HHV to interfere with cytokine-mediated feed-forwarding activity. Using an EBV, wild-type strain that expresses 13 v-miRs and a deletion strain lacking any miRs, they demonstrated that v-miRs can modulate various pathways including apoptosis, cell cycle, cytokine signaling, and antigen processing relevant to viral persistence [47]. Further examples of the role of v-miR in immune evasion via altered chemotaxis can be found in HCMV (See **Table 2**).

Table 2. The list of v-miR targets involved in the antigen processing and presentation and T-cells activation and polarization.

Viral miR	Target	Functional impact	References
HCMV miR-UL112; EBV miR-BART-2-5p; KSHV miR-K12-1	MICB	NK cells/CD8+T-cell/$\gamma\delta$ T cells cytosolic evasion by reducing stimulatory signals through NKG2D receptor.	[48]
HCMV miR-US25-2-3p	TIMP3	Degradation of MICA and hence reduced NKG2D activation.	[49]
BHRF1-3; BART17	TAP2	Blocks peptide transport	[47]
EBV miR-BART2 BHRF1-2	CTSB	Interferes with MHC class I antigen processing.	[47]
EBV miR-BART1-5p; BART3; BART15; BART16; BART17-5p	LMP1	Downregulation of highly immunogenic viral latency membrane protein 1.	[50]
EBV miR-BART22	LMP2A	Downregulation of highly immunogenic viral latency membrane protein 2A.	[51]

Continued

EBV miR-BART2	LCMN	Reduced processing of MHC-II bound pathogenic antigens.	[47]
EBV miR-BART1	IFI30	Inhibition of MHC class II restricted antigen processing.	[47]
EBV BART1; BART2; BART10; BART22; BHRF1	IL12B	Prevents polarization of Th cells to antiviral Th1 subtype.	[47]
HCMV-UL-148D	CCL5	Reduced NK cell activation and T-cells recruitment.	[52]
EBV BHRF1-3	CXCL11	Inhibition of chemotaxis of activated T-cells.	[53]

4. Viral miRNA and Exosome Pathway

Viruses use a clever strategy to spread their genetic influence inside the body. Just like human cells, viruses can package their viral microRNAs (v-miRs) into tiny, membrane-bound vesicles called exosomes (20 - 100 nm in size). These exosomes travel between cells, delivering viral molecules that can manipulate host cell functions [54]. Viruses take advantage of this system to shut down important immune responses, helping them survive in the body. Unlike viral proteins, v-miRs do not trigger an immune response, giving viruses an advantage. Research shows that viruses like Epstein-Barr Virus (EBV) use exosomes to transport v-miRs, such as miR-BART-15, which suppresses inflammation by targeting NLRP3, a key immune regulator. This helps the virus avoid detection and persist in the body. Similarly, studies on Human Cytomegalovirus (HCMV) reveal that viral particles (virions) carry both viral and cellular RNAs. Researchers found that HCMV virions contain 14 viral miRNAs and two cellular miRNAs, suggesting that viruses selectively pack these molecules into virions. These viral miRNAs can be functionally delivered to new host cells, where they silence specific genes to benefit the virus [55]. In summary, viruses use both exosomes and virions to spread their miRNAs, allowing them to control host cell functions, evade immune responses, and persist in the body.

5. Conclusions

Human Herpesviruses (HHVs) remain a significant global health concern due to their ability to establish lifelong infections, evade the immune system, and contribute to a wide range of diseases. Our understanding of their molecular mechanisms, particularly their interactions with host cells, has grown considerably. However, challenges such as viral latency, reactivation triggers, and immune evasion strategies continue to complicate treatment and prevention efforts. Advances in molecular biology and virology have shed light on how these viruses manipulate host cellular pathways, particularly through viral proteins and microRNAs. These findings open new avenues for targeted therapies and vaccine development. De-

spite these advances, HHVs continue to pose a challenge, particularly in immunocompromised individuals where reactivation can lead to severe complications. Current antiviral treatments focus primarily on managing symptoms and reducing viral replication, but they do not eliminate the virus. Therefore, a deeper exploration of viral-host interactions, particularly at the epigenetic and immunemodulatory levels, is crucial for developing more effective therapeutic strategies.

Future Perspectives

The future of HHV research lies in a multidisciplinary approach combining virology, immunology, genomics, and bioinformatics to develop innovative therapeutic strategies. Several promising areas of research include:

- **Targeting Viral microRNAs (miRNAs):** Since miRNAs play a crucial role in modulating host responses and viral latency, therapies targeting these small regulatory molecules could offer novel antiviral strategies. CRISPR-based gene editing and RNA interference (RNAi) hold potential in silencing viral miRNAs to prevent viral replication and reactivation.
- **Host-Directed Therapies:** Instead of directly targeting the virus, modulating host factors essential for viral survival could offer an alternative approach. Investigating host proteins and pathways that facilitate HHV persistence may lead to the development of small-molecule inhibitors or immunotherapies that enhance the body's ability to clear infections.
- **Vaccine Development:** While vaccines exist for some HHVs (such as varicella-zoster virus), developing effective vaccines for other types like Epstein-Barr virus (EBV) and cytomegalovirus (CMV) remains a challenge. Advances in mRNA vaccine technology, as seen during the COVID-19 pandemic, may provide new opportunities for herpesvirus vaccine development.
- **Next-Generation Antiviral Drugs:** Current antiviral drugs primarily target viral DNA replication. The development of novel inhibitors that interfere with viral proteins involved in immune evasion and latency maintenance could offer more effective treatment options.
- **Artificial Intelligence and Bioinformatics in Viral Research:** Machine learning and computational modeling can help predict viral mutations, identify potential drug targets, and enhance our understanding of herpesvirus evolution. These tools will be instrumental in guiding future research and therapeutic interventions.

Relevant Techniques: Throughout my research on Herpesvirus-encoded miRNAs and their role in host-virus interactions, I have reviewed a range of molecular and bioinformatics techniques [56]. These include:

- **MicroRNA Sequencing & Profiling:** To identify and characterize viral and host miRNAs involved in infection and pathogenesis [56].
- **Quantitative PCR (qPCR) & RT-PCR:** For validation of differentially expressed miRNAs and their target genes.
- **RNA Immunoprecipitation (RIP) Assays:** To confirm interactions between viral miRNAs and their target mRNAs.

- **Next-Generation Sequencing (NGS) Data Analysis:** Using bioinformatics tools for miRNA and mRNA target prediction and pathway analysis.
- **Cell Culture & Viral Infection Models:** Working with herpesvirus-infected cells to study gene expression changes.
- **Western Blot & Immunoassays:** To assess protein-level changes influenced by viral miRNAs.

These methodologies have provided critical insights into how herpesviruses exploit miRNAs to modulate host immune responses and maintain viral persistence.

Conflicts of Interest

The author declares no conflicts of interest.

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Abbreviations Used

TLRs: Toll-Like Receptors
PRRs: Pathogen Recognition Receptors
HCMV: Human Cytomegalovirus
HSV: Herpes Simplex Virus
EBV: Epstein-Barr Virus
KSHV: Kaposi's Sarcoma Herpes Virus
BoHV: Bovine Herpesvirus
APC: antigen presenting cells
BART: BamHI fragment A rightward transcript
BHRF1: BamHI fragment H rightward reading frame 1
C/EBP: CCAAT-enhancer-binding proteins
CCL5: chemokine (C–C motif) ligand 5
CREBBP: CREB-binding protein
CTL: cytotoxic T lymphocyte
ERAP1: endoplasmic reticulum aminopeptidase 1
IFI30: interferon gamma-inducible protein 30
IFN: interferon
IKK: inhibitor of kappa B kinase
IL: interleukin
IRAK1: interleukin-1 receptor–associated Kinase
IRF: interferon regulatory factor
LAT: latency-associated transcript
LMP: latency-associated membrane proteins
MHC: major histocompatibility complex
MICA/MICB: MHC class I polypeptide-related sequence A/B
MyD88: myeloid differentiation primary-response gene
NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells
NLR: nucleotide oligomerization domain (NOD)-like receptors
NLRP3: NLR family, pyrin domain containing 3
PAMP: pathogen associated molecular patterns
PEL: primary effusion lymphoma
RLR: retinoid acid-inducible gene-I (RIG-I)-like receptors
SOCS2: suppressors of cytokine signaling 2
Th: T helper
TIMP: tissue inhibitor of metalloproteinases
TNF: tumor necrosis factor
TWEAKR: TNF-like weak inducer of apoptosis receptor
UTR: untranslated region