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The Roles of Non-coding RNA in HSV Infection

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ABSTRACT

Herpes simplex virus (HSV) is a spherical virus with a high infection rate, and its lifelong infection characteristics are related to its survival strategy. Non-coding RNA (ncRNA) is a type of RNA that is only transcribed and not translated into protein. In the process of HSV infection, ncRNAs, including miRNAs and lncRNAs, play an important role. HSV virus use these ncRNAs, derived from themselves or kidnaped from host cells, to regulate its life cycle, including the replication, latent and reactivation. Host cells also use these ncRNAs, especially miRNAs, as their defense and protection strategies. In this review, we summarized the important ncRNAs found during HSV infection. Understanding the function and mechanism of these ncRNAs is important for prevention and treatment of the diseases caused by HSV infection.

INTRODUCTION

Herpes simplex virus (HSV) is a spherical virus composed of capsule, interstitial protein, nucleocapsid and genomic DNA. [1] It is an important infectious virus and causes many diseases worldwide. In many countries, the infection rate of HSV is close to 100%. [2] HSV infection is lifelong for host, which gives it opportunities to maximize its spread to more hosts and thus take advantage of evolution [3].HSV infection has two types: latent infection and lytic infection [4].Usually, latent infection accounts for the majority and lytic infection is self-limiting. The HSV genome contains approximately 90 transcription units, of which at least 84 encode proteins with linear temporal expression: immediate early gene (ffi), early gene (E) and late gene (L) [5-7]. During HSV latent infection, HSV limits the expression of its own genes, expressing only non-coding viral RNAs called Latent-Associated Transcripts (LATs), while simultaneously reducing the expression of soluble genes to near undetectable levels to escaping the host attack by the immune system [8-11]. HSV is mainly divided into two types, hsv1 and hsv2 [1]. HSV-1 usually infects the face area and then infects the sensory neurons of the Trigeminal Ganglion (TG) lifetimely; whereas HSV-2 infection usually occurs in the genital area, after which HSV2 will established the lifelong infection in sensory neurons of the dorsal root ganglia [12].

Non-coding RNAs are a class of untranslated RNAs, which are divided into small non-coding RNAs and long non-coding RNA (lncRNA) according to their molecular size. MiRNA belong to small ncRNA and it was originally found in Caenorhabditis elegans and expressed in a variety of eukaryotes [13]. The molecular size of mature miRNA is

about 21-23 nucleotides, which processed by Dicer from a single-stranded RNA precursor about 70-90 bases in size with a hairpin structure [14]. Majorly through binding with 3'UTR of genes to regulate their expression, miRNAs are involved in almost all cellular processes, such as cell cycle, cell migration, and host response to viral infections [15,16]. lncRNAs are a class of non-coding RNAs over 200 nucleotides in length that play important roles in gene transcription, post-transcriptional regulation (mRNA cleavage and translation), and epigenetic regulation [17]. Without exception, the replication, latent and reactivation of HSV virus and the response of host cells to HSV infection are also regulated by Non-coding RNA, whether they come from a host or a virus. Understanding the specific mechanisms of non-coding RNA function in HSV infection will help us to prevent and treat the diseases caused by HSV.

miRNAs and HSV

Many reports reveal that miRNAs affect the life cycle of HSV, including its replication, latency and activation processes. The viral miRNA can inhibit the expression of certain important genes by targeting down-regulation of viral mRNA or host mRNA, which helps HSV enter the latent state and evade the host's immune defense. The expression of the host's miRNA also varies greatly before and after HSV infection, indicating that the host miRNA also plays a role in the lifespan of HSV [18].

miRNAs regulate replication of HSV

The replication process of HSV is related to the state in which it is located. In some respects, inhibition of HSV replication is beneficial to maintain its latent state. The replication of HSV is regulated by two aspects, one is the self-regulation of the virus inside, and the other is the regulation by the host cell. miRNAs derived from the virus itself and host cells have a large impact on the viral replication process.

Viral miRNAs regulate HSV replication: When HSV start to replicate themselves, them will meet some inhibition from host cells. For example, the cells produced transcriptional repressor, Kelch-like 24 (KLHL24), can inhibit the immediate transcriptional efficiency of the viral immediate early and early genes. Through generating hsv1-mir-H27 to block the expression of KLHL24 in cells, HSV-1 reduces the inhibition from host cells, conducive to efficient replication and proliferation [19]. In addition to up-regulating replication of HSV, miRNAs also involved in the down-regulation of HSV replication. Two HSV-1 derived miRNAs, miR-H28 and miR-H29, produced in the late stage of HSV-1 infection, accumulate in neurons during reactivation of the virus from latent state, which reduce the accumulation of viral mRNA and protein and decreases the plaque size [2]. Here HSV use HSV derived miRNAs as tool to speed up or slow down its replication. This is a useful strategy for its survival.

Host cellular miRNAs regulate HSV replication: Host cells also use cell derived miRNA to inhibit HSV replication as their defense and protection strategies. The miRNAs usually target the host cellular genes that express some of the core proteins involved in the HSV replication process, through post-transcriptional regulation. G-Rich Sequence Factor 1(GRSF1) is a protein belongs to the RNA-binding protein family, which involved in HSV-1 replication and increase the replication of HSV-1 by enhances its translation by binding to HSV-1 mRNA. During HSV-1 infection, ICP4 from the virus directly binds to the miR-101-2 / RCL1 promoter to activate its expression and induce expression of miR-101 in HeLa cells; miR-101 directly binds to the 3'UTR of GRSF1 mRNA, specifically reduces target gene expression, finally inhibiting GRSF1 expression during HSV-1 infection process [20]. There are more than one target for miR-101. It has been reported that miR-101 can also directly bind to the 3'UTR region of mitochondrial ATP synthase subunit β (ATP5B) to down-regulating ATP5B expression. ATPB is a subunit of F1 ATP synthase located in the mitochondrial inner membrane, and its knockdown significantly inhibits the replication of HSV-1 [21]. HSV also can kidnap miRNAs derive from host cells to help its switch from replication to latent or to promote its replication. Mucosa associated lymphoid tissue lymphoma translocation gene 1 (MALT1) expresses an upstream protein that affects NF-κB activation and nuclear translocation [22,23] MiR-649 can directly target the 3'-UTR of MALT1 to regulate its expression [24]. This maybe a regulative mechanism of keeping homeostasis of the NF-κB signaling in the cells. Because NF-κB activation can inhibit HSV-1 replication, during HSV-1 infection, host cells down-regulate the expression of miR-649 to enhance the expression of MALT1 and the signaling of NF-κB pathway, finally inhibit HSV-1 replication. This may be a strong strategy of host cells against viral infection, or a method can be used by HSV-1 to maintain a low infection level for better latent survival strategy [24]. Jing Ru et al. found that

miR-23a binds to the 3'UTR of the innate antiviral Interferon Regulatory Factor 1 (IRF1) and downregulates its expression, thereby reducing the expression of the radical S-adenosyl methionine domain containing 2 (RSAD2). RSAD2 plays an important role in the interferon induced antiviral state of host cells. In HSV-1 infected HeLa cells, miR-23a peaked 18 hours after infection and HSV-1 replication enhanced by MiR-23a up-regulation [25]. Similarly, HSV-1 infection can up-regulate the expression of miR-373 in cells, which can directly down-regulate the expression of IRF1through binding with its target site located in the 3'UTR of IRF1, finally inhibit IRF1 induced expression of type I IFN [26]. When IFNI binds to the receptor, it activates the downstream Jak-Stat pathway and up-regulates the expression of more than 300 Interferon-Stimulated Genes (ISG), which plays a role in pathogen clearance. [27,28] MiR-373 promoting HSV-1 replication through affects IFN-1 production and ISG expression [26]. The miRNAs in host cells play complex roles. They may help host cells to inhibit HSV infection, or be kidnap by HSV to enhance viral replication or to help HSV entering latent condition via down-regulating its replication.

miRNAs play roles in HSV latency and activation

The LAT gene family is located in the connected region of the long terminal repeat TRL, IRL, and the long unique sequence ML in the HSV genome. As the only gene family abundantly expressed in the HSV latency, miRNAs expressed by the LAT gene is essential for the in the incubation period and reactivation process of HSV [29]. The conversion of HSV from latent to productive infection requires some gene-specific expression to produce certain proteins. The early viral proteins ICP0, ICP4, and ICP34.5 all play important roles in this process. Many miRNAs affect the latency status changes of HSV by affecting the expression of these proteins.

Viral miRNAs regulate HSV latency and activation: Some proteins play an important role in the latent or lytic process of HSV, such as ICP4. It is required for HSV to produce lytic infections. As a viral trans-activator, it down- regulates gene expression through interaction with RNA polymerase II-related transcription factors, and negatively regulates many miRNAs encoded by LAT [30]. Controlling the expression of these miRNAs and their viral targets contributes to HSV latency and reactivation [31-33]. ICP0 is a virus immediate early protein, as a lytic gene activator, which degrades some cellular proteins through the protein-proteasome pathway, thereby slowing the inhibition of viral transcription by cells. [34] ICP0 also inhibits Histone Deacetylases (HDACs) and Promyelocytic Leukemia Proteins (PML) that could promote viral gene expression in low-virulence-infected cells [35-38]. ICP34.5 is a protein kinase R inhibitor that acts as a key viral neurovirulence factor and also contributes to viral replication in neurons [39-42]. Inhibition of these proteins that activate viral cleavage is important to maintains the latent state of the virus, which is consistent with HSV survival strategies. After infecting host cells, HSV-1 virus produces virus derived miRNA, miR-H6, it can inhibit the expression of ICP4 to inhibit HSV-1 infection in HCE cells and reduce IL-6 production [43]. Dongli Pan et al. found a HSV-1 miRNA miR-H2, a weak inhibitor of ICP0 expression, can reduce the expression of ICP0 mRNA and protein in transfected cells, and alleviate HSV-1 neurovirulence and viral reactivation [44]. Shuang Tang et al. found that the HSV-2 LAT-associated miRNA miR-I is located on the antisense strand of ICP34.5, and can specifically reduces the expression of ICP34.5 by siRNA mechanism [45]. They also found miR-II, which has a similar function to miR-I, also silences ICP34.5 expression, then identified another miRNA miR-III, it can silences ICP0 expression [31].

Host cellular miRNAs regulate HSV latency and activation: HSVs are often subtly adapted to host miRNA mechanisms after infection of host cells, using host miRNAs to evade immunity or maintain latency. For example, HSV-1 infection results in increased expression of miRNA-146a in human brain cells and down-regulation of its target complement factor H [46]. This suggests that HSV-1 can escape complement activation, which is a major first-line host defense mechanism. MiR-138 from neurons binds to two target sites in ICP0 mRNA when cell infected by HSV-1, inhibits the expression of ICP0, leads to decreased expression of lytic genes, and maintains HSV-1 latency by preventing cell lysis from dying [38]. These miRNAs utilized by HSV may not have been designed to perform these functions, and exploring their function in host cells may be beneficial in responding to HSV infection. In addition, we can also use these miRNAs as targets to treat HSV infections in a targeted manner.

miRNAs with other functions associated with HSV: There are also some miRNAs that do not play a role in the replication or

infection of HSV but play different roles in their respective life processes, such as affecting the development of disease or regulating the production of blood vessels. Corneal angiogenesis is an important pathological process for the eye. HSV-1 infection leads to up-regulation of IL-17 in the cornea, IL-17 increases the level of vascular endothelial growth factor VEGF in the eye, and VEGF acts through the VEGFR2 receptor on vascular endothelial cells, via cAMP response element binding protein (CREB) and up- regulation of miR-132 expression; miR-132 removes Ras-GAP (an intrinsic inhibitor of Ras), resulting in activation of angiogenic Ras and corneal neovascularization [47]. HSV-1-encoded miR-H1 specifically targets ubiquitin protein ligase E3 component n-recognin 1 (Ubr1), and silencing Ubr1 -mediated ubiquitin-proteasome protein degradation via the Arg / N-terminal regulatory pathway, which enhances the accumulation of denatured proteins (such as Aβ) in nerves, may lead to the acceleration of neuropathy [48].

Some miRNAs are closely related to diseases caused by HSV infection, and their expression changes before and after HSV infection have a great influence on the state of the disease. Bunsoon Choi et al. found that the level of miR-21 was associated with inflammation in Behçet's Disease (BD) model mice and BD patients. Down-regulation of miR-21 causes down-regulation of IL-17 and IL-6, and attenuates HSV-induced BD-like inflammation [49]. In addition, HSV infection has a chance to cause herpes simplex encephalitis (HSE), and it has been reported that miR-155 knockout mice have reduced CD8 T cell responses and are more prone to HSE or herpes zoster lesions, indicating miR-155 plays an important role in the development of HSE, so miR-155 can be considered as an early warning molecule for HSE [50,51].

lncRNAs and HSV

lncRNAs are also involved in HSV replication and viral gene expression processes. Nuclear Paraspeckle Assembly Transcript 1 (NEAT1) is an important long non-coding RNA associated with Dengue Disease and a crucial structural platform for paraspeckles [52-54]. HSV-1 infection increases NEAT1 expression in a STAT3-dependent manner. NEAT1 acts as a scaffold to promote the interaction of the paraspeckle component P54nrb and PSPC1 with viral genes, increasing viral gene expression and replication; Knockdown of NEAT1 also has a limiting effect on skin damage caused by HSV-1 infection, suggesting that NEAT1 may serve as a potential target for limiting HSV replication [55,56]. It has been reported that there are more than 500 differentially expressed lncRNAs in HSV-1 infected HIFF cells, but the mechanism of action of lncRNA associated with HSV is rarely reported [57]. As an important class of non- coding RNA, lncRNA is likely to play a more important role in the life process of HSV.

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Table 1: ncRNAs play different roles in HSV replication and infection

Name	Type	Origin	Target
mir-H27	miRNA	HSV-1	KLHL24
miR-H28	miRNA	HSV-1	\
miR-H29	miRNA	HSV-1	\
miR-H6	miRNA	HSV-1	ICP4
miR-H2	miRNA	HSV-1	ICP0
miR-H1	miRNA	HSV-1	Ubr1
miR-I	miRNA	HSV-2	ICP34.5
miR-II	miRNA	HSV-2	ICP34.5
miR-III	miRNA	HSV-2	ICP0
miR-101-2	miRNA	Host cell	GRSF1 / ATP5B
miR-649	miRNA	Host cell	MALT1
miR-23a	miRNA	Host cell	IRF1
miR-373	miRNA	Host cell	IRF1
miR-146a	miRNA	Host cell	complement factor H
miR-138	miRNA	Host cell	ICP0
miR-132	miRNA	Host cell	Ras-GAP
miR-21	miRNA	Host cell	\
miR-155	miRNA	Host cell	\
NEAT1	lncRNA	Host cell	\