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Functions of miRNA in Animal Viral Infection

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Abstract: miRNAs participate in multiple biological processes of an organism. Virus is closely related to miRNA in the course of infection. This study aimed to determine the interaction between host and virus-encoded miRNA in the course of infection based on virus-encoded miRNA's regulation of its own gene, virus-encoded miRNA's regulation of host gene. The effect of viral infection on expression of host-encoded miRNA was also investigated.

Key words: miRNA, viral infection, regulation, organism, virus

INTRODUCTION

miRNA is a type of non-coded RNA with a length of 22 nucleotides (nt) that is widely found in animals and plants. The miRNA is used as target molecule to perform biological functions by cutting and degrading mRNA, inhibiting protein interpretation and regulating gene expression. miRNA is found in early *Caenorhabditis elegans* (Lee *et al*., 1993). Lin-4 which is related to the development of C. *elegans* is gradually receiving considerable attention (Wightman *et al*., 1993). Studies have proven that miRNA participates in physiology, pathology, organism development, cell differentiation, proliferation and other biological processes (Geeleher *et al*., 2012; Sun *et al*., 2013; Zhang *et al*., 2013).

Pfeffer *et al*. (2004) identified the virus-encoded miRNA in his research on herpesvirus for the first time. The total number of virus-encoded miRNAs exceeds 490 and this number is continuously increasing (Grundhoff and Sullivan, 2011; Klase *et al*., 2013; Steitz *et al*., 2010) (Table 1). In the course of evolution, host can react with viruses through miRNA.

GENERATION AND MECHANISM OF VIRUS-ENCODED miRNA

miRNA generation: The course of animal virus miRNA generation is similar with the host. miRNA is transcribed from noncoding regions of the genome to initial miRNA (pri-miRNA) by RNA polymerase II or III (Diebel *et al*., 2009). Pri-miRNA is similar to mRNA in that it is a protein-encoded gene with a 5' capped and 3' polyadenylation tail structure and a length of several thousand bases (Shapiro *et al*., 2012). Pri-miRNA is cut to miRNA precursor (pre-miRNA) with a length of approximately 70 nt and a stem-loop structure using a compound consisting of drosha (Lin *et al*., 2010). Pre-miRNA was transferred from the nucleus into the cytoplasm using Ran-GTP-dependent cytoplasmic transport protein exportin 5 (Han *et al*., 2013; Leisegang *et al*., 2012). The pre-miRNA is then cut to acquire an incomplete pairing of double-stranded (ds) RNA with a length of 21-25 nt using dicer. dsRNA is a dimer composed of mature miRNA and miRNA*. miRNA* is a section of RNA in pre-miRNA and its position is exactly the opposite of that of mature miRNA. Finally, the RNA-Induced Silent Complex (RISC) is produced with mature miRNA and argonaute protein and the miRNA* was degraded (Slezak-Prochazka *et al*., 2010) (Fig. 1).

Mechanism of miRNA: miRNA facilitates the degradation of target mRNA and the inhibition of interpretation. mRNA is induced to achieve full or nearly full complementary pairing for RNA degradation, inhibition of interpretation is achieved as non-fully complementary pairing. The degree of inhibition is related to the loci of miRNA combined with target mRNA. The majority of miRNAs combined with the non-interpretation area of

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Table 1: Summary of virus-encoded microRNAs (From http://www.mirbase.org/cgi-bin/browse.pl)

Virus	No. of validated mature miRNAs	No. of validated pre-miRNAs	Size (nt)	References
Bovine herpesvirus 1	12	10	20~24	Glazov *et al.* (2010)
BK polyomavirus	2	1	22	Seo *et al.* (2008)
Bovine leukemia virus	10	5	20~23	Kincaid *et al.* (2012) and Rosewick *et al.* (2013)
Duck enteritis virus	33	24	19~24	Yao *et al.* (2012)
Epstein Barr virus	44	25	20~24	Cai *et al.* (2006), Landgraf *et al.* (2007) and Pfeffer *et al.* (2004)
Herpes B virus	15	12	21~23	Amen and Griffiths (2011)
Human cytomegalovirus	26	15	21~24	Dunn *et al.* (2005), Landgraf *et al.* (2007), Meshesha *et al.* (2012) Pfeffer *et al.* (2005) and Stark *et al.* (2011)
Human immunodeficiency virus 1	4	3	20~24	Lin and Cullen (2007), Omoto and Fujii (2005), Omoto *et al.* (2004) and Pfeffer *et al.* (2005)
Herpes simplex virus 1	27	18	20~24	Jurak *et al.* (2010), Tang *et al.* (2008) and Umbach *et al.* (2008, 2009)
Herpes simplex virus 2	24	18	18~22	Jurak *et al.* (2010)
Herpesvirus saimiri strain A11	6	3	21	Cazalla *et al.* (2011)
Herpesvirus of turkeys	28	17	21~26	Waidner *et al.* (2009)
Infectious laryngotracheitis virus	10	7	20~24	Rachamadugu *et al.* (2009) and Waidner *et al.* (2009)
JC polyomavirus	2	1	22	Seo *et al.* (2008)
Kaposi sarcoma-associated herpesvirus	25	13	22~24	Cai *et al.* (2005), Cai and Cullen (2006), Lin *et al.* (2010) and Umbach and Cullen (2010)
Mouse cytomegalovirus	29	18	20~23	Buck *et al.* (2007)
Merkel cell polyomavirus	2	1	22	Seo *et al.* (2009)
Mareks disease virus	26	14	20~24	Morgan *et al.* (2008) and Yao *et al.* (2008)
Mareks disease virus type 2	36	18	20~23	Waidner *et al.* (2009)
Mouse gammaherpesvirus 68	28	15	18~25	Diebel *et al.* (2009), Landgraf *et al.* (2007), Pfeffer *et al.* (2005), Reese *et al.* (2010) and Zhu *et al.* (2010)
Pseudorabies virus	13	13	19~22	Wu *et al.* (2012)
Rhesus lymphocryptovirus	68	36	19~24	Cai *et al.* (2006) and Riley *et al.* (2010)
Rhesus monkey rhadinovirus	11	7	19~24	Schafer *et al.* (2007)
Simian virus 40	2	1	20	Sullivan *et al.* (2005)

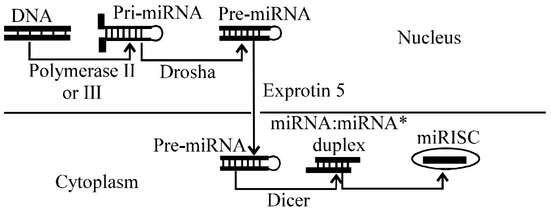

Fig. 1: The biogenesis of miRNAs. miRNA are transcribed from noncoding regions of the genome to initial miRNA (pri-miRNA) by RNA polymerase II or III. Pri-miRNA is cut to miRNA precursor (pre-miRNA) with a length of approximately 70 nt and a stem-loop structure using a compound consisting of drosha. Pre-miRNA is transferred from the nucleus into the cytoplasm using exportin 5. The pre-miRNA is then cut to acquire an incomplete pairing of double-stranded (ds) RNA with a length of 21-25 nt using dicer. Finally, the RNA-Induced Silent Complex (RISC) is produced with mature miRNA and argonaute protein and the miRNA* was degraded

target mRNA at 3'. Some miRNAs could be combined with the 5' Untranslated Region (UTR) or the Open Reading Frame (ORF) of target mRNA (Bartel, 2004). In animal cells, the majority of miRNAs downregulate gene expression through inhibiting interpretation, however in plant cells, miRNA participates in mRNA degradation (Carrington and Ambros, 2003).

Some virus-encoded miRNAs: The herpesvirus family comprises three subfamilies, namely, α, β and γ herpesvirus. Studies showed that these subfamilies can encode a mass of miRNAs. Epstein-Barr Virus (EBV) is the first virus which was verified to encode miRNA. Five miRNAs are cloned from B cells with dormant infection of EBV (Lin and Flemington, 2011; Pfeffer *et al.*, 2004). These five miRNAs were found in B95-8 virus strains which were divided into two genomic clusters (Koshiol *et al.*, 2011). One cluster is located in the *BHRF-1* gene. The miR-BHRF-1 is located in the 5' UTR of the *BHRF-1* gene whereas miR-BHRF-1-2 and miR-BHRF-1-3 are located in the 3' UTR of the *BHRF-1* gene (Koshiol *et al.*, 2011). Another cluster included miR-BHRF-1 and miR-BHRF-2 which are located in the *BART* gene (Kramer *et al.*, 2011; Murphy *et al.*, 2008). Moreover, related studies on rat γ herpesvirus and Kaposi's sarcoma virus also proved that these viruses can encode miRNAs (Landgraf *et al.*, 2007; Pfeffer *et al.*, 2005).

Recent studies found fourteen miRNAs in Marek's Disease Virus (MDV) genome. Among these miRNAs, five are distributed around the *Meq onco* gene and three are located in the potential-related transcript area. Northern analysis proved that eight miRNAs are expressed in MDV-infected cells or tumors caused by MDV (Burnside *et al*., 2006). These miRNAs are speculated to be related to tumor formation. Human Cytomegalovirus (HCMV), Herpes Simplex Virus-1 (HSV-1), Herpes Simplex Virus-2 (HSV-2) and mice cytomegalovirus have been proven to encod miRNA (Klase *et al*., 2013; Libri *et al*., 2011; Sarid and Gao, 2011; Veksler-Lublinsky *et al*., 2012).

People have recently become increasingly aware of the Human Immunodeficiency Virus (HIV-1). Nef protein is an HIV-1-encoded protein that can aid in the long-term survival of infected cells (Witkowski and Verhasselt, 2013). A type of viral-encoded miRNA, named miR-N367, is separated from HIV-1-infected MT-4T cells and nef-transduced cells which is located at the conservative area (420-443 nt) of the virus-encoded *nef* gene (Sisk *et al*., 2012).

EFFECT OF VIRUS-ENCODED miRNA DURING INFECTION

Effect of virus-encoded miRNA on virus: Virus-encoded miRNA can decrease relative protein expression by degrading early protein or main antigen mRNA, downregulating the protein mRNA needed for viral replication or inhibiting the interpretation of virus mRNA to prevent the immunological recognition of a virus (Boss and Renne, 2010, 2011; Xiang *et al*., 2012). Herpes Simplex Virus I (HSV-1) can encode HSV-1-miR-H2-3P and HSV-1-miR-H6 after infection. At the early stage, HSV-1-miR-H2-3P and HSV-1-miR-H6, respectively act on the rapid transcription activator ICP0 and ICP4 which is related to viral replication and activation (Halford *et al*., 2001; Jurak *et al*., 2010). Thus, the host immune response is effectively evaded. EBV-encoded miR-BART-1-5p can effectively down regulate the expression of immune reaction-related recessive membrane protein 1, thereby causing the host to be recessively infected (Lo *et al*., 2007). Compared with mild virus, mutant strain SV 40 of non-codable miRNA can more easily be killed by the immune cells of the host (Gee *et al*., 2010; Sullivan *et al*., 2005).

Regulation of virus-encoded miRNA: During a viral infection, a virus can rapidly and effectively regulate and control down stream genes by regulating the miRNA of host (Carl *et al*., 2013). Thus, the up regulation and down regulation of some miRNAs in the host occur during viral infection (Ouellet *et al*., 2013). Some viruses encode miRNAs by themselves through the host gene to inhibit the resistance of host to the virus, thereby weakening the immune reaction of host (Bakre *et al*., 2012; Wang *et al*., 2012). Some viruses have directional effects on the host gene by encoding miRNA to change the expression of the host gene, thereby making the host environment more suitable for virus survival (Li *et al*., 2011). During HIV infection, the expression levels of miR-17-5a and miR-20a expression are down regulated (Ouellet *et al*., 2008). This down regulation results in the increased expression of Tat cofactor PCAF which enhances HIV infection (Shapshak, 2012; Zhou *et al*., 2012). HCMV-encoded miRNA HCMV-miR-UL112 can reduce the expression level of the MHC-related chain B protein ligand 1 of Natural Killer (NK) cell activation receptor 2D (Hoffmann *et al*., 2012). Thus, the possibility of being killed by NK cells is reduced. HIVmiR-N367 can inhibit virus transcription by acting on the negative response element in 5'-LTRU3 and reducing the active 5'-LTR promoters in human T cells to maintain continuous infection (Ouellet *et al*., 2008). Researchers investigating HCMV found that the virus strain from HCMV-miR-UL112 mutation can easily be identified and killed by NK cells compared with the wild strain (Shimakami *et al*., 2012). Thus, HCMV-miR-UL112 participates in the interaction between the virus and host. Some studies found that Kaposi's sarcoma virus-encoded miR-K12-3 can inhibit the expression of cell liver-inhibitory proteins (Liang *et al*., 2011).

EFFECTS OF HOST-ENCODED miRNA ON VIRAL INFECTION

Anti-virus action of host-encoded miRNAs: Upon entry into host cells, parasitic viruses can replicate and multiply using the life mechanism of host (Kumar *et al*., 2009). An environmental change in the host can affect viral replication. The host-encoded miRNA regulates viral replication through direct or indirect action on the virus gene (Jeang, 2012; Veksler-Lublinsky *et al*., 2012). This action widely occurs in mammals and serves a positive or negative regulatory function in viral replication (Song *et al*., 2010). Human cell-encoded miRNA-32 can effectively inhibit and regulate the replication of prototype foamy virus by regarding a foamy virus genome ORF 2 as a target. Studies found that human T cell-encoded miRNA can target the entire HIV genome. The miR-29a and miR-29b can target the *nef* gene, miR-149 can target the *vpr* gene, miR-378 targets the *env* gene and miR-324-5p targets the *vif* gene (Zhang *et al*., 2012). These target sequences are highly conservative in all HIV envelope sequences (except for the envelope). Given that defects in the *nef* gene are closely related to long-term non-pathogenesis status of a virus, researchers speculate that the miRNA level is the critical factor in disease development after HIV-1 infection.

Positive action of host-encoded miRNAs during viral replication: In addition to negative regulation, the miRNA of host had a positive regulatory effect on viral infection (Orom *et al*., 2008; Vasudevan *et al*., 2008). Liver specificity miR-122 is directly related to HBV replication. If miR-122 was inhibited, 80% of HBV could not be replicated. Research showed that miR-122 can promote Hepatitis C Virus (HCV) replication *in vitro* in combination with the non-interpretation area at HCV 5' (Jin *et al*., 2007).

CONCLUSION

Viruses live parasitically in cells and are replicated and multiplied by substances in cells. The smooth replication of a virus depends on the ability of a virus to use the life events of host for replication and multiplication (Li *et al*., 2011; Scaria *et al*., 2006; Steitz *et al*., 2010; Zhao *et al*., 2012). In this stage, host can affect the replication and multiplication of viruses through their own regulatory mechanisms. Host can inhibit viruses using miRNA through RNA silencing. Moreover, a virus can prevent the inhibition of host by encoding some inhibiting factors including small RNA molecules and proteins (Gottwein and Cullen, 2008; Umbach and Cullen, 2009) (Fig. 2).

With the growing body of research, an increasing number of miRNA molecules have been foundand more miRNA-related mechanisms have been explained. Host and viruses can encode miRNA and mediate the interaction between a virus and cell. New ideas and methods are needed to understand viral infections and their potential mechanismsand discover new anti-virus pathways. By combining different viruses, the interaction between host and virus-encoded miRNAs can be explained at different infection stages which facilitates understanding of the pathogenesis of viruses and prevents viral diseases.

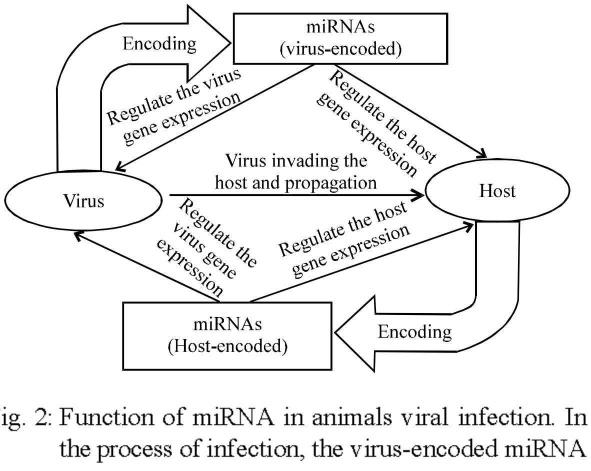

Fig. 2: Function of miRNA in animals viral infection. In the process of infection, the virus-encoded miRNA could regulate the expression of the host and the host-encoded miRNA affect the activities of the virus

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