miRNAs: Biogenesis, Origin and Evolution, Functions on Virus-Host Interaction

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Abstract
MicroRNAs (miRNAs) are small endogenous non-coding functional RNAs. They can play vital roles in post-transcriptional regulating mRNAs transcripts in nearly all biological processes. More and more reports on miRNAs come from different species (animal, plant, bacteria, virus) in the researches in development, immunity, apoptosis, tumor, virus-host interaction. These recent findings provide new insights into the roles of miRNAs as well as their function. This review outlines the ever-deepening understanding of miRNAs (biogenesis, origin, evolution), and discusses functions from host and viral miRNAs in the context of virus-host interaction.

Introduction
As small endogenous non-coding RNAs, microRNAs (miRNAs) can recognize and bind mRNA transcripts in a sequence-specific mode, finally resulting in degradation or translation termination of the corresponding mRNAs [1, 2]. Since the first discovery of miRNA (lin-4) from nematode cell [3], so far 24521 miRNAs (or pri-RNAs) have been identified or characterized from plant, animal, bacterium, virus species (Release20, miRBase). As an important post-transcriptional regulator of gene expression, miRNAs help to confer robust control on biological processes to maintain considerable homeostasis in transcript copy.
number, which bring important consequences on normal development and physiology, disease, and evolution [4].

miRNAs have several striking features that are listed as below: (1) Small molecule. miRNAs are evolutionally conservative, non immunogenic RNAs with an approximate length of 22 nucleotides (nt) containing a seed region (positions 2-8nt from the 5’-end of miRNA) [5]; (2) Big mighty. miRNAs play vital roles in development, cell differentiation, apoptosis, innate immunity, molecular metabolism based on post-transcriptionally and dynamically negative regulation [2, 6-8]; (3) High efficiency. On average, an individual miRNA can regulate more than 100 target genes, meanwhile, more than 50% mRNAs transcripts can be coordinately co-regulated by more than two miRNAs (Fig. 1), forming an precise and complex regulation system or network [2, 8, 9]; (4) Diverse binding sites. miRNAs can specifically bind to 3’-untranslated regions (3’ UTR) [10], 5’ UTR [9, 11] or encoding region of mRNAs transcripts [12]; (5) Various pathways of miRNA biogenesis. The pathways of miRNAs biogenesis appear common and individual among animals, plants and viruses or even within species (See below) [2, 13].

With the rapid development of molecular technologies and bioinformatics softwares, more and more miRNAs have been identified, functionally analyzed or characterized. Most significantly, deep sequencing (or high through sequencing) technique extremely accelerates the progress of miRNAs investigation, which could finish sequence analysis of several thousands or even million species of DNA fragments in one reaction [14, 15]. Presently, miRNAs functions are mainly investigated based on some approaches as repression or over-expression of miRNAs [16]. Relevant softwares (MiRscan/RNAfold/miRNA Targets etc.) and databases (miRBase, RepTar) provide a strong support to identify miRNAs as well as their target genes [17-19].

Various Pathways of miRNA Biogenesis

Canonical miRNAs biogenesis in animal undergo stepwise processes: (1) miRNA loci transcription and further processing to precursor transcripts (pri-miRNA) by RNA polymerase II and related proteins factors; (2) The conversion of pri-miRNA to precursor miRNA (pre-miRNA) by Drosha (RNaseIII-like enzyme) complex; (3) Transportation of pre-miRNA into cytoplasm from nuclus by Exportin5 complex (with Ran-GTPase activity) [20]; (4) Generation of an approximately 21-22nt RNA duplex structure (miRNA/miRNA*) by Dicer (with RNaseII-like enzyme activity) [21]. Subsequently, miRNA (also called guide strand) is preferentially incorporated into a silencing complex (RNA induced silencing complex, RISC), which recognizes and binds to specific mRNA transcript by partial base pairing [10]. miRNA* (also called passenger strand) is typically assumed to be merely a carrier strand, which is finally degraded and is therefore non-functional [22]. Nevertheless, updated data disclose Drosophila melanogaster miRNA* has substantial influence on miRNA and 3’ UTR evolution by associating with Argonaute proteins [23]. Another example is miR-31*, a highly conserved miRNA across mammals [22]. It can down-regulate RhoA expression by targeting the 3’ UTR of RhoA, and seemly counteract the functions of miR-31 during oral squamous cell carcinoma (OSCC) tumorigenesis [24].

Plants miRNAs biogenesis undergo a similar conversion from pri-miRNA to pre-miRNA to RNA duplex (miRNA/miRNA*) [13, 25]. Likewise, plant pri-miRNAs are also primarily transcribed by RNA polymerase II to produce RNA-like structure with 5’-end cap and 3’-end polyA tails. Differently, the pri-to-pre-miRNA conversion and mature miRNA processing in plants are performed based on interaction between DCL1 (instead of Drosha-like enzyme in animals) and two proteins (HYL1 and SE) in nuclear processing centers, which are called D-bodies or SmD3/SmB-bodies [26-28]. Moreover, plant miRNA/miRNA* duplex is generated in nuclus and then directly transported into cytoplasm by HASTY (a plant homolog of Exportin-5), while animal miRNA/miRNA* duplex occurs in cytoplasm derived from a pre-miRNA generated in nuclus and transported into cytoplasm by Exportin-5.
protein. Additionally, the size of plant pri-miRNAs hairpins usually ranges from 70 to several hundreds of bases, while that of animal pri-miRNAs hairpins is from 55 to 70nt with an exception of 200nt from pri-miRNAs in *Drosophila* (Release20, miRBase).

Viral miRNAs biogenesis mainly depends on host-related proteins or enzymes. Most viruses adopt a strategy similar to host cell to generate viral pri-miRNAs by host RNA polymerase II. These viral pri-miRNAs are further processed to pre-miRNAs by the host Microprocessor complex. Notably, Herpesvirus saimiri (HVS) can produce Sm-class U RNAs (HSURs) by RNA Pol II in latently-infected marmoset T cells. Experiment data support the idea that HVS utilizes the host integrator complex instead of Microprocessor complex to generate pre-miRNAs hairpins [29]. Exceptionally, some viral pri-miRNAs are primarily transcribed by host RNA polymerase III such as bovine leukemia virus (BLV) [30, 31] and murid herpesvirus 4 (MuHV-4) [32]. Another view believes that certain viral miRNAs (such as from mouse γ-herpesvirus 68, MHV68) are derived from larger tRNA-like precursor structures transcribed by host polymerase III (tRNase Z) [33, 34]. In addition, a part of animal pri-miRNAs are also transcribed by RNA polymerase III [35].

**Location, Origins and Evolution of miRNAs**

*Location of miRNAs loci*

miRNA genes are located in the genome with several possibilities: (1) within protein encoding region, mostly in introns. This is the frequent case in metazoan. These miRNAs genes often occur in clusters, orient on the same DNA strand of the host gene, and are co-transcribed as polycistronic RNAs [36-38]. The miRNA-host co-expression implies that intronic miRNAs can silence genes that are functionally antagonistic to their host genes [39] or facilitate their host genes by mediating synergistic and antagonistic regulatory effects [40]. Latest data show that young intragenic miRNAs are less co-expressed with host genes than old ones, implying co-evolution between miRNAs and their host genes [41], (2) within intergenic region (mostly in plants). Plants miRNAs genes generally tend to be clustered. They are primarily transcribed as a single primary transcript, and further processed in a stepwise mode into individual precursors [13, 42]. Comparative genomic analysis in three plants (rice, poplar and *Arabidopsis*) discloses that miRNA clusters usually encode miRNAs of the same family, and frequently share a common evolutionary origin. Most clusters contain hairpins encoding identical mature miRNAs, implying increase of the dosage of a particular

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**Fig. 1.** Possible highly efficient regulation modes of miRNAs. (Notes: A represents that certain miRNAs loci could generate identical miRNAs, which improves the dose of the same miRNA; B discloses an individual miRNA could bind and negatively regulate two or more mRNAs; C shows one mRNA could be regulated by two or more miRNAs).
miRNA for stronger function. Non-homologous miRNAs from the same cluster are proposed to target transcripts encoding functionally related proteins [43].

In general, miRNA(s) loci are single-directionally transcribed to produce pri-miRNA(s). Accumulating evidences demonstrate that, a part of miRNAs loci can be bi-directionally transcribed [18, 44]. For example, the iab-4 miRNA locus is bi-directionally transcribed to two primary miRNAs transcripts. Further analysis finds that bi-directional transcription of the iab-4/8 locus and production of miRNAs from both transcripts are conserved in insect species [44]. Besides, bi-directional transcription and processing of the Hox mir-iab/mi-iab-8 locus may generate four functionally different miRNAs including two miRNA* [23, 45, 46].

Origin and evolution

Presently, there are several popular views on the origin of miRNAs. In the first one, it is believed that miRNAs genes may originate from duplication and nucleotide substitution of old miRNA genes [47]. In the second one, it is proposed that miRNAs come from inverted terminal repeats of transposable elements (TEs) [26, 48]. And, the third describes miRNAs genes may come from random hairpin structures in intronic or intergenic regions [49, 50]. Recently, Nozawa et al. suggest that gains or losses of miRNAs genes frequently occur during evolution of 12 Drosophila species, and these new miRNAs genes mainly originate from random hairpin structures in intronic or intergenic regions as well as duplication of miRNAs genes [51]. Subsequently, Nozawa et al. propose duplication of preexisting miRNA genes or protein-encoding genes may be the major evolutionary mode in 11 plant species, while transposable elements also additionally generate species-specific miRNAs genes [1]. Obviously, the mode of miRNAs origination is quite different between Drosophila and these 11 plants species. Further analysis reveals that young miRNAs genes are less conserved than old ones in plants as well as in Drosophila species. Moreover, the repertoires of miRNAs genes change more dynamically based on some genes families loss during plants evolution.

In addition, newly arisen miRNAs genes appear similar nucleotide substitution rate to that of synonymous nucleotide sites in protein encoding genes, implying that most new miRNAs genes evolve almost neutrally, and have not acquired any substantial function [1]. Which arm of the hairpin precursor (5’ or 3’ arm) could be finally processed into mature miRNA? Marco et al. believe there is a bias toward 5’ or 3’arm usage for a given miRNA; Significant shifts in arm usage frequently occur, which are likely to change target profile and therefore function of a given miRNA during insect evolution [52]. It is also very likely that seed shifting (changes in the 5’ end of miRNA) also can alter significantly targets of the cell.
mature miRNAs [53]. Actually, seed shifting is as frequent as arm switching during evolution. These two phenomena affect about 1/5 of all miRNAs conserved between *Drosophila* and *Tribolium* [52].

### miRNAs Regulation on Virus-host Interaction

To date, about 800 viral miRNAs (or miRNA precursors) have been reported (Release 20 in miRBase and recent investigation), most of which are from DNA viruses (Table 1). Whereas, increasing evidences indicate that RNA viruses also encode miRNAs [54-57]. Recent studies confirm that baculovirus (such as BmNPV, *Bombyx mori* nucleopolyhedrosis virus, a kind of double-strand DNA virus) also generates miRNAs [58, 59], which suppress its host miRNAs biogenesis by regulating the exportin-5 cofactor Ran [58].

As importantly regulatory molecules, miRNAs play vital roles in virus-host interaction whatever from viral miRNAs or cellular miRNAs, both of which form considerable complex regulatory network (Fig. 2) [31, 60, 61]. On the one hand, while viral miRNAs auto-regulate viral miRNAs transcripts [62], they also down-regulate host miRNAs transcripts to facilitate

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**Table 1.** Virus-encoded miRNAs or Pre-miRNAs. (Notes: The data in table came from miRBase (Release20) and recent investigation. Notably, the data in miRBase is constantly updating because, on the one hand, new pre-miRNAs and miRNAs will be continually identified or characterized, and on the other hand, the available data is also continually revised based on new investigation)

| Virus                                      | Pre-miRNA | Mature miRNA |
|--------------------------------------------|-----------|--------------|
| Bovine herpesvirus 1                       | 10        | 12           |
| BK polyomavirus (BKV)                      | 1         | 2            |
| Bovine leukemia virus                      | 5         | 10           |
| Bandicoot papillomavirus carcinoma virus type 1 | 0        | 1            |
| Bandicoot papillomavirus carcinoma virus type 2 | 0        | 1            |
| Duck enteritis virus                       | 24        | 33           |
| Epstein Barr virus                         | 25        | 44           |
| Herpes B virus                             | 12        | 15           |
| Human cytomegalovirus                      | 15        | 26           |
| Human herpesvirus 6B                       | 0         | 8            |
| Human immunodeficiency virus 1             | 3         | 4            |
| Herpes Simplex Virus 1                     | 18        | 27           |
| Herpes Simplex Virus 2                     | 18        | 24           |
| Herpesvirus saimiri strain A11             | 3         | 6            |
| Herpesvirus of turkeys                     | 17        | 28           |
| Infectious laryngotracheitis virus         | 7         | 10           |
| JC polyomavirus (JCV)                      | 1         | 2            |
| Kaposi sarcoma-associated herpesvirus      | 13        | 25           |
| Mouse cytomegalovirus                      | 18        | 29           |
| Merkel cell polyomavirus                   | 1         | 2            |
| Mareks disease virus                       | 14        | 26           |
| Mareks disease virus type 2                | 18        | 36           |
| Mouse gammaherpesvirus 68                   | 15        | 28           |
| Pseudorabies virus                         | 13        | 13           |
| Rhesus lymphocryptovirus                   | 36        | 68           |
| Rhesus monkey rhadinovirus                 | 7         | 11           |
| Simian virus 40 (SV40)                     | 1         | 2            |
| *Bombyx mori* nucleopolyhedrosis virus     | 4         | 4            |
| Heliothis viresens ascovirus               | 1         | 1            |
| Total                                      | 300       | 498          |
viruses’ evasion from monitoring of the host defense system [63, 64], or to prevent host cell apoptosis [65, 66], or to delay or stop host cell cycle [9, 67]. On the other hand, host miRNAs also exert a profound impact on virus replication because host miRNAs expression profiles change dramatically during virus infection [68-72].

**Viral miRNAs share high homologies and similar functions with host miRNAs**

Viral miRNAs, with high homologies to host miRNAs, can “cheat” host cells or directly “take over” pre-existing regulatory pathways of host miRNAs. B-cell tumors are strongly affected in cattle by BLV infection (bovine leukemia virus, a kind of RNA virus). BLV encodes a conserved cluster of miRNAs transcribed by the RNA polymerase III (pol III). BLV-miR-B4 shares sequence identity and common targets with the host miRNA (miR-29). B-cell neoplasms induced by miR-29 overexpression resemble BLV-associated tumors. Therefore, BLV-miR-B4 is regarded as ortholog of miR-29, which contributes to BLV-induced tumorigenesis [31].

miR-155 plays diverse roles in the biology of lymphocytes [73-75], and it could coordinately repress a broad range of genes such as the PU.1, BACH-1, and CEBPβ genes with other miRNAs [73]. So miR-155 is closely associated with lymphoid malignancies and the modulation of immune responses. Viral miRNA miR-K12-11, encoded by KSHV (Kaposi’s Sarcoma Associated Herpesvirus), shares high homology with cellular miR-155. The data support that miR-K12-11 or miR-155 can down-regulate an extensive set of common mRNA targets, implying viral miR-K12-11 can function as an ortholog of cellular miR-155. Therefore, miR-K12-11 may contribute to the induction of KSHV-positive B-cell tumors in the infected patients [76].

A kind of naturally occurring neoplastic disease of poultry, called Marek’s disease (MD), usually results from causative MDV (Marek’s disease virus). Genetically modified MDV with and deletion of six-miRNA cluster 1 from the viral genome, could abolish the oncogenicity of the virus in chickens. Further analysis discovers that miR-4, in six-miRNA cluster 1 in MDV genome, functions as ortholog of cellular miR-155 to inhibit lymphomas. Related evidences also support the role of viral miR-4 as cellular miR-155 ortholog based on rescue experiment of oncogenic phenotype by relevant viruses expressing either the miR-M4 or the cellular homolog gga-miR-155 [77-79].

**Viral miRNAs facilitate to counteract apoptosis, establish and maintain viral latency**

The latency-associated transcript (LAT) is regarded as the only viral protein expressed during infection in neurons induced by herpes simplex virus-1 (HSV-1). It could counteract apoptosis and maintain latency by promoting the survival of infected neurons [80]. mir-LAT, encoded by the HSV-1 LAT gene, sharing partial homology with 3’ UTR of transforming growth factor (TGF-β) and SMAD3, can down-regulate expression of TGF-β1 and SMAD3, both of which are functionally linked in the TGF-β pathway [66]. Previous data implies that TGF-β is a potent inhibitor of cell growth and an inducer of apoptosis [81]. Viral miRNA regulates the induction of apoptosis in infected cells by modulating TGF-β signaling, and thus contributing to the persistence of HSV in a latent form in sensory neurons [66]. LAT gene at least encodes 4 distinct miRNAs in HSV-1 infected cells. Of the 4 miRNAs, miR-H2-3p can auto-regulate viral transcript of ICP0 (a viral immediate-early transcriptional activator), which is an important protein in productive HSV-1 replication and reactivation from latency [82]. Moreover, the fifth HSV-1 miRNA, miR-H6 (not from LAT gene transcript) is also identified to inhibit transcript of ICP4 (another HSV-1 transcription factor in charge of expression of most HSV-1 genes) in latently infected trigeminal ganglia. Therefore, miRNAs encoded by HSV-1 in latently infected neurons, can regulate viral genes expression to facilitate the establishment and maintenance of viral latency [83]. HIV-1 produces TAR
viral miRNA [84], and the TAR miRNA down-regulates cellular genes involved in apoptosis to protect infected cells from apoptosis, especially for genes of ERCC1 (Excision repair cross complementing group 1) and IER3 (Intermediate early response 3) [57]. Other studies also confirm that herpesvirus miRNAs play important roles during persistent or latent infection in infected host cell [63, 67].

miR-US25-1, encoded by human cytomegalovirus (HCMV), is proven to have multiple cellular targets which are involved in cell cycle control, such as cyclin E2, BRCC3, EID1, MAPRE2, and CD147. Deletion of miR-US25-1 from HCMV results in over expression of cyclin E2 in the context of viral infection, which facilitates viruses to block cell cycle progression at the G1/S phase. miR-US25-1 seed matches binding sites occur within 5' UTRs instead of 3' UTRs of mRNAs transcripts based on RISC-IP techniques (RNA induced silencing complex immunoprecipitation) [9].

Viral miRNAs facilitate to evade host immunology system monitoring

Viral miRNA, encoded by simian virus 40 (SV40), is firstly identified to auto-regulate viral transcript, and decreases the expression of viral T antigens. However, it fails to reduce the yield of infectious virus compared with that generated by a mutant lacking SV miRNAs. Further analysis shows that wild-type SV40-infected cells are less sensitive than the mutant to lysis by cytotoxic T cells, revealing viral evolution enhances the probability of successful infection by miRNA [62].

The major histocompatibility complex class I-related chain B (MICB) is a stress-induced ligand of the natural killer (NK) cell activating receptor NKG2D, which is critical for the killing of virus-infected cells and tumor cells. Hcmv-miR-UL112, encoded by human cytomegalovirus (HCMV), can specifically down-regulate MICB and perturb its binding with NKG2D during viral infection, which consequently facilitate NK attack evasion. Viruses can directly exploit their miRNAs to down-regulate host immune defense genes to evade from the monitoring by host immunology system. Moreover, a novel view is proposed that a viral miRNA (hcmv-miR-UL112), together with a viral protein (HCMV UL16), cooperatively targets the host MICB protein [85].

Polyoma viruses BKV and JCV, a kind of small DNA viruses, establish asymptomatic persistent infection in 65-90% of humans, and can cause severe illness under immunosuppressive conditions [86]. Recent investigation represents a viral miRNA, identical in sequence with JCV and BKV, can target the stress-induced ligand ULBP3, a protein recognized by the killer receptor NKG2D. Viral miRNA-mediated ULBP3 down-regulation results in reduced NKG2D-mediated killing of virus-infected cells by natural killer (NK) cells. Briefly, JCV and BKV use an identical miRNA that targets ULBP3 to escape detection by both the innate and adaptive immune systems, explaining how these viruses remain latent without being eliminated by the immune system [87].

Host miRNAs also actively regulate virus replication

To regulate transcription factors

miR-132, a widely investigated cellular miRNA, is highly up-regulated during CD4(+) T cell activation, facilitating HIV-1 replication in the Jurkat CD4(+) T cell line. miR-132 can target MeCP2 (Methyl-CpG binding protein 2, a transcriptional regulatory protein), and can inhibit MeCP2 mRNA and protein levels [68]. Previous investigation also reveals that, miR-132 is highly up-regulated and targets the transcript of co-activator P300 to regulate the host antiviral innate immune response when host cell is infected by Kaposi's sarcoma herpesvirus (KSHV), herpes simplex virus-1 (HSV-1), and human cytomegalovirus (HCMV) [71]. So miR-132 can potentiate viral replication by inhibiting expression of mRNAs of the related transcription factors.
To stimulate viral translation

mir-122, a liver-specific miRNA, interacts with two target sites in the 5′-UTR of the Hepatitis C virus (HCV) genome, and stimulates HCV translation by enhancing the association of ribosomes with the viral RNA at an early initiation stage, making a contribution to HCV liver tropism at translation level [72]. Recent study shows that, Argonaute (Ago) 2 protein directs mir-122 binding to HCV RNA, which improves HCV RNA stability and translation stimulation [69]. Roberts et al (2011) [88] also believe that mir-122 activates HCV translation via the HCV 5′-UTR. And, mir-122 regulation is a highly specialized process, which requires uncapped RNA, the HCV internal ribosome entry site (IRES) and the 3′ region of mir-122 [88]. Disputably, other views are proposed that translation activation does not involve a structural transition in the HCV IRES and is mediated by Argonaute proteins [69, 72].

To inhibit host innate immunity

mir-155 is usually over-expressed in many tumors. EBV-infected B cells could be transformed into indefinitely proliferating lymphoblastoid cell lines (LCLs), where several cellular miRNAs are usually produced (such as mir-21, mir-155 and mir-146a). mir-155, the most highly expressed miRNA, is associated with B-cell lymphomas. Selective inhibition of mir-155 specifically prevents the growth of LCLs while cells lacking mir-155 fail to progress through S phase and spontaneously undergo apoptosis [89]. The EBV-encoded latency membrane protein 1 (LMP1) is a potent activator of NF-B signaling pathways. LMP1 is essential for EBV immortalization of B lymphocytes, which can up-regulate mir-155 in human B lymphocytes. Previous investigation represents that mir-155 contributes to EBV immortalization by modulating NF-B signaling and suppressing of host innate immunity to latent viral infection [90].

Conclusions

Rapidly accumulating data significantly broaden our knowledge on miRNAs biogenesis origin and evolution, functions. Moreover, novel findings of miRNAs are continually proposed one after another: (1) miRNAs could “buffer” developmental programs against variation and confer robustness to diverse regulatory networks [4, 91]; (2) Some miRNAs (such as miR-146a, miRNA-101) could act as effective biomarkers for diagnosis, prognosis or therapeutic molecules [92, 93]; (3) The finding of baculovirus miRNAs will arouse inspiration in investigators to deeply explore highly efficient biological pesticides at miRNAs level [58]; (4) Especially for miRNAs on host-virus interaction, related studies have opened a door to the development of attenuated virus vaccines, which can grow in and kill cancer cells but spare adjoining normal cells [6, 94, 95]. Therefore, miRNAs have become gradually the focus in the exploration of regulation in gene expression, a promising approach to tumor diagnosis and therapy as well as a valuable method to seek highly efficient bio-insecticides.

However, the functions of most miRNAs remain unclearly. Even for those miRNAs well characterized functionally, their roles in the context of real physiological states in vivo need to be intensively explored, because miRNAs function are obtained mainly based on approaches that alter the normal physiological surrounding of miRNAs by over-expression or inhibition expression of miRNAs. Furthermore, several troublesome problems need to be solved such as identification and functional analysis of low abundance of miRNA (or miRNA*) etc. So, there is still a long way to go for comprehensive understanding of miRNAs regulatory mechanism as well as their applications on clinical diagnosis and therapy, insect management etc.

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