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A Review of the Interaction between miRNAs and Ebola Virus

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ABSTRACT

Ebola virus (EBOV) is a life-threatening and virulent pathogen that kills approximately 90 percent of infected individuals. Nowadays, microRNAs (miRNAs) have become a promising option for more efficient screening, diagnosis, monitoring, and therapy of numerous diseases such as cancer, stroke, Alzheimer's, and viral infections. Recent studies have revealed the role of EBOV and host-encoded miRNAs in Ebola virus disease (EVD), opening an avenue for developing novel drugs against EVD and diagnostic panels for EBOV infection. EBOV-encoded miRNAs such as miR-VP-3p and miR-1-5p and anti-EBOV host cell miRNAs such as has-miR-150-3p, has-miR-103b and has-miR-145-3p might be a possible diagnostic biomarker or druggable targets. This paper highlights the importance of viral and cellular miRNAs in EBOV infection and EVD.

Keywords: Ebola virus, MicroRNAs, virus diseases

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Introduction

In recent years, microRNAs (miRNAs) have attracted the attention of many researchers. They are a broad family of small, non-coding single-stranded RNAs with a length of 17–24 nucleotides that constitute a principal part of the RNA interference (RNAi) system (Figure 1) (1). Generally, about 60 percent of human gene regulation is attributed to miRNAs (2). Each miRNA regulates hundreds of targets (3). miRNAs play important roles in physiological processes and their deregulation was reported in many pathological conditions, such as carcinogenesis, anoikis resistance, metastasis, and viral infections (2, 4-7). Cellular miRNAs play a crucial role in the life cycle of several viruses (8) such as human papillomavirus (HPV) (9-11), human cytomegalovirus (HCMV) (12-14), Epstein-Barr virus (EBV), hepatitis B virus (HBV) (15), hepatitis C virus (HCV) (16), influenza A virus (FluA) (17), human T-cell leukemia virus type 1 (HTLV-1) (18, 19), human immunodeficiency virus (HIV) (20). In addition, it has been established that some viruses encode their own v-miRNAs and others use cellular miRNAs (21, 22). In EBV, BamHI-A antisense transcripts (BARTs) encode for a large number of v-miRNAs. Some of them target the 3′UTR of EBV latent membrane protein 1 (LMP-1), and it has been indicated that LMP-1 has a key role in the induction of nasopharyngeal carcinoma (NPC) (23). Moreover, miR-H1 in HIV-1 targets transcript of apoptosis antagonizing transcription factor (AATF) that downregulates c-myc, B-cell lymphoma 2 (Bcl-2), and Dicer expression. This miRNA also reduces the expression of cellular miR-149 that targets HIV-1 Vpr protein. Taken together, miR-H1 disrupts cellular responses to HIV-1 infection (24).

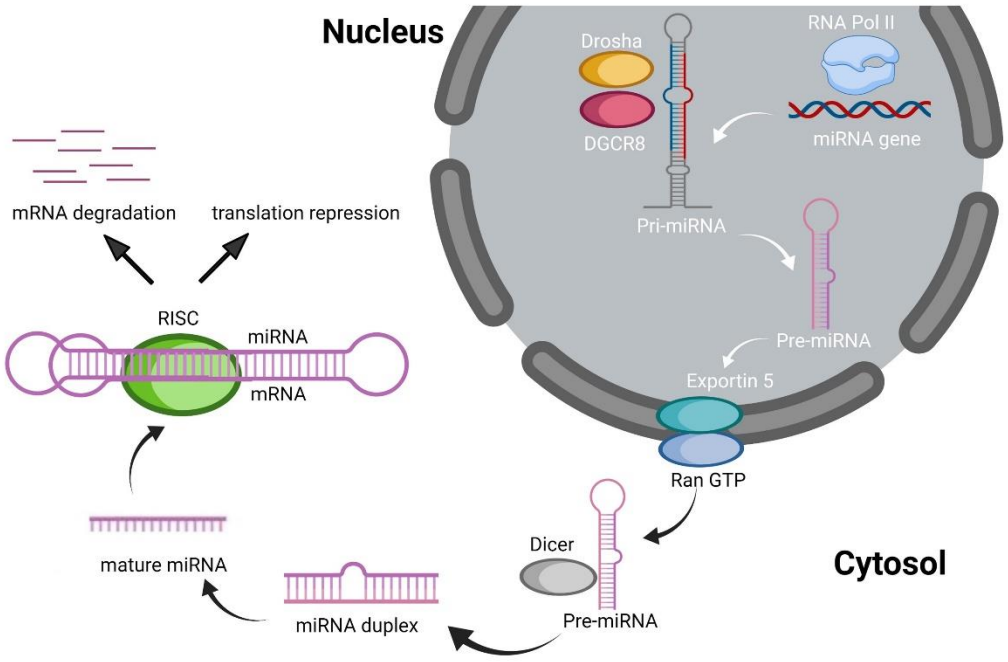

Fig. 1. miRNA biogenesis. RNA polymerase II produces a primary miRNA, or pri-miRNA. In the next step, pri-miRNA is matured by the DGCR8-Drosha complex, which is converted to pre-miRNA. The pre-miRNA is transported to the cytoplasm by Ran-GTP/exportin 5. In the cytosol, pre-miRNA is cleaved and converted into a miRNA duplex by Dicer. After the miRNA-miRNA duplex unwinds, one strand (mature miRNA) is loaded into RISC, and the complementary strand is removed. The mature miRNA guided the RISC to target mRNA. The mature miRNA binds to target mRNA, leading to mRNA degradation.

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Cellular miRNA regulates antiviral response-related signaling pathways. hsa-miR-192 and hsa-miR-215 target the frizzled receptors, while hsa-miR-181a directly binds to β-catenin (CTNNB1) in Wnt- β-catenin pathway during Rotavirus infection (RV) but their expression downregulated during RV infection leading to activated Wnt/β-catenin signaling and survival of infected cells. On the other hand, combined overexpression of miR-192 and miR-215 in RV-infected cells inhibited Rotavirus replication. miR-34 family also downregulate the Wnt pathway repressing flavivirus replication and enhance the interferon response in infected cells(25).

The p38 MAPK pathway is activated during IAV infection and its suppression inhibited of IAV and Respiratory Syncytial Virus (RSV) viral replication. miR-124a, miR-744, and miR-24 show extensive antiviral effects against IAV and RSV such as downregulation of MK2 and p38 MAPK reduced activation. During coxsackievirus (CVB3) infection of HeLa cells, miR-21 upregulation, downregulated MAP2K3 and suppressed p38 MAPK signaling pathway leading to viral progeny release inhibition and reduced cellular apoptosis(25, 26).

Among the viral infections, miRNAs possess potential important functions in Ebola virus (EBOV) infection. EBOV is a linear, non-segmented, negative-stranded and enveloped RNA virus that belongs to the filoviridae family (27). The viral proteins include glycoprotein 1,2 (GP1,2), nucleoprotein (NP), VP35 (polymerase cofactor), VP40 (matrix protein), VP30 (transcriptional activator), VP24 (RNA complex-associated protein), and L (large protein) (28). To date, based on the International Committee on Taxonomy of Viruses (ICTV), six species in the genus of ebolavirus have been identified, including Bombali EBOV, Bundibugyo EBOV, Reston EBOV, Sudan EBOV, Tai Forest (formerly: Côte d'Ivoire) EBOV, and Zaire EBOV (29). EBOV infection drives cytokine storm (high-level production of pro-inflammatory cytokines), disseminated intravascular coagulation (DIC), disabling of lymphocyte immune response, and host T cell apoptosis that consequently leads to Ebola virus disease (EVD) or Ebola hemorrhagic fever (EHF). Clinical manifestations include fever, chills, headache, sore throat, muscle aches, vomiting, diarrhea, maculopapular rash, impaired kidney/liver function, and internal/external bleeding (30). The largest-ever epidemic of EVD has been ongoing in West Africa since 2016, with more than 11,000 deaths (31).

Literature Searching

In this paper, we systematically searched scientific repositories, including Medline/PubMed and Web of Science, to identify relevant studies. We used a combination of keywords including ("Ebolavirus") OR ("Ebola virus") OR ("EBOLA") AND ("microRNA") OR ("miR") OR ("miRNA"). A total of 10 articles were included in this review. We have summarized the current resources highlighting the importance of both cellular and v-miRNAs in EBOV infection and disease.

miRNA and Ebola virus infection

RNA viruses replicate in the cytoplasm of the host cell. Theoretically, because of their lack of access to the nucleus, these viruses cannot encode v-miRNA. However, there are several reports indicating that West Nile Virus (WNV) (32), Dengue virus (DENV) (33), and Influenza A virus produce v-miRNAs (34-36). Liang HW et al. decided to answer the question: Can EBOV encode functional miRNAs or miRNA-like small RNAs? In 2014, this group used computational prediction followed by experimental validation methods and demonstrated that the EBOV genome produces two putative v-miRNA precursors (EBOV-pre-

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miR-1 and EBOV-pre-miR-2) and three putative mature microRNAs. They validated this feature in human embryonic kidney 293T (HEK293T) cells transfected with a pcDNA6.2-GW/EmGFP-EBOV-pre-miRNA plasmid and concluded that EBOV-miRNAs are generated by the cellular-miRNA processing complex. Surprisingly, they showed that Sudan and Zaire EBOVs encode these miRNAs but not Reston EBOV (37), consistent with the high mortality rate of Sudan EBOV and Zaire EBOV and the low mortality rate of Reston EBOV (38). Cellular target prediction analysis elucidated that the expression of host genes involved in virus immune escape and apoptosis can be regulated via EBOV-miRNAs. Also, EBOV-miRNAs can be utilized as a biomarker for the diagnosis and prognosis of EBOV infection and as a novel molecular target for EVD therapy (37). EBOV glycoprotein (GP) is a player in the inflammation, cell cytotoxicity, immune system impairment, detachment of endothelial cells (Anoikis), and increased vascular permeability seen in EVD (39-41). Another work, using next-generation sequencing (NGS) and differentially expressed miRNAs (DEmiRs) analysis, opened more detailed insight into EBOV pathogenesis. It showed that EBOV GP upregulates host cell miRNAs: hsa-miR-1246, hsa-miR-196b-5p, and hsa-miR320a in human umbilical vein endothelial cells (HUVECs), and subsequently downregulates their target genes (associated with cell adhesion): tissue factor pathway inhibitor (TFPI), caspase 8 and FADD-like apoptosis regulator (CFLAR), and dystroglycan1 (DAG1) at the protein level. Eventually, these events lead to increased vascular permeability, loss of endothelial cell integrity, and EHF. This research also introduced inhibitors of hsa-miR-320a, hsa-miR-1246, and hsa-miR-196b-5p as novel potential EBOV infection therapeutics that effectively reduced EBOV cell cytotoxicity (42). A group of researchers used a systematic genome-wide screening (an approach that is different from the Liang HW method) to find the potential miRNAs in the EBOV during the 2014 EBOV outbreak. They predicted and experimentally confirmed seven mature EBOV-miRNAs (including EBOV-miR-T1-5p, EBOV-miR-T1-3p, EBOV-miR-T2-5p, EBOV-miR-T2-3p, EBOV-miR-T3-3p, and EBOV-miR-T4-3p) and their target genes. The target genes that are downregulated by these v-miRNAs include nuclear factor kappa B (NF-KB) and tumor necrosis factor (TNF) involved in virus-cell crosstalk, viral replication, immune evading, and apoptosis (43). A computationally-based analysis of human miRNAs found ten human miRNAs (hsa-miR-5699-5p, hsa-miR-4682, hsa-miR-4692, hsa-miR-548az, hsa-miR-145-3p, hsa-miR-4526, hsa-miR-548s, hsa-miR-491-3p, hsa-miR-3065-5p, and hsa-miR-4633-3p) that can potentially block EBOV infection via degradation of viral transcripts (44). Northern blotting analysis of the sera of EVD patients revealed the presence of a miRNA-like RNA fragment corresponding to miR-VP-3p in the serum specimens of EVD patients but not in healthy individuals. They further utilized reverse transcription-polymerase chain reaction (RT-PCR), TA-cloning, and sequencing techniques to validate the presence of this miRNA-like RNA fragment. Then, the presence of EBOV-miR-VP-3p was confirmed. The result of miR-VP-3p measurement in the sera of EBOV RNA RT-PCR-negative EVD patients detected a high level of miR-VP-3p, suggesting that miR-VP-3p could be detected before the EBOV RNA became positive. Thus, miR-VP-3p can be utilized as a useful biomarker for the fast diagnosis of EBOV cases, which fills the gap in the field of EBOV diagnostics and helps the control of future EBOV outbreaks (45). Importin-α5 plays a role in the nuclear accumulation of signal transducer, activator of transcription-1 (STAT-1), and interferon (IFN) signaling. The importance of IFN in viral infection, evasion, and pathogenesis is indispensable (46-49). Yuanwu Liu *et al*. identified a v-miRNA

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named Zebov-miR-1-5p (similar to hsa-miR-155-5p) that is encoded at the 5′-UTR of the VP24 EBOV gene and downregulates importin-α5 (KPNA1) expression, which may impair IFN signaling and induce viral pathogenesis (50). Current EBOV diagnostic methods are usually limited to viral detection and cannot identify asymptomatic or presymptomatic cases; therefore, alteration of all host RNA transcripts (transcriptome) induced by EBOV infection can be a good surrogate option. A retrospective investigation of the expression of 752 circulating miRNAs in longitudinally collected plasma specimens from rhesus macaques challenged EBOV via intramuscular (IM) injection and aerosol inhalation, as well as plasma samples of EBOV-infected patients (during the 2014 outbreak in Western Africa), discovered 36 miRNAs differentially expressed in human and non-human primate (NHP) groups. Fifteen of them were markedly correlated to the EBOV viral load in both non-human primates and human samples. Also, a miRNA panel was developed by using 8 selected miRNAs (including hsa-miR-146a-5p, hsa-miR-18b-5p, hsa-miR-21-3p, hsa-miR-22-3p, hsa-miR-29a-3p, hsa-miR-432-5p, hsa-miR-511-5p, and hsa-miR-596) that correctly classified infection status in 64/74 (86%) human and non-human primate samples. This classifier detected acute infections in 27/29 (93.1%) samples and 6/12 (50%) presymptomatic non-human primates (51). In 2018, the minigenome system, tetracistronic transcription, and replication-competent virus-like particle (trVLP) system, along with RT-PCR, western blot, and double fluorescence reporter assays, were used for screening of anti-EBOV host miRNAs. The results exhibited that miR-150-3p, miR-103b, and miR-15a-3p had the best inhibitory effect against EBOV infection. Among them, miR-150-3p blocked the reproduction of trVLPs by directly targeting the coding sequences of GP and VP40 and regulating the expression of GP and VP40 (52). Analysis of mouse, rhesus macaque, cynomolgus macaque, and humans infected cells with EBOV using the RT-PCR method revealed that miR-1-5p, miR-1-3p, and miR-T3-3p had the highest expression level, which may pose an important function in EBOV pathogenesis and can be exploited as a useful diagnostic marker (53). The eye is one of the immune-privileged body sites (which have suppressed and/or completely blocked immune responses to foreign antigens) (54). It was previously shown that eye retinal pigment epithelial cells are a potential reservoir for EBOV in the human eye. Persistent EBOV in the eye can lead to uveitis (an inflammatory condition that leads to swelling and destruction of eye tissue), which is considered a sequela in EVD survivors. Uveitis occurs in approximately a quarter of EVD survivors. RNA sequencing of the human retinal pigment epithelial cell line (ARPE-19) infected with EBOV revealed 13 miRNAs that were markedly upregulated (such as hsa-miR-29b-3p, hsa-miR-33a-5p, and hsa-miR-1307-5p) and 2 miRNAs that were markedly downregulated (hsa-miR-27b-5p, and hsa-miR-3074-3p). Also, EBOV-miR-1-5p was detected in this EBOV-infected cell line. The targets of these miRNAs function in the innate and adaptive immune system, cell apoptosis, autophagy, and neuroinflammation (55). Quantitative PCR (qPCR), small RNA sequencing (sRNA-Seq), and functional assessment were conducted on the human liver cell line (Huh7) infected with EBOV to identify the comparative miRNA transcriptome (miRNome). The obtained results elucidated the miRNA-based immunity pathways and provided new insights into the molecular signature of human liver cells following EBOV infection, which can be used as a biomarker for fast and timely diagnosis (56). A study has been carried out on host-miRNA responses in the Cynomolgus macaque model using blood samples that were longitudinally collected during the EVD course to find biomarkers. Identified miRNA biomarkers were related to dysregulated host immune

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responses in EVD. In particular, hsa-miR-122-5p and hsa-miR-125b-5p interact with immunological genes that regulate both B-cell and T-cell activation. These miRNAs are potentially valuable as novel diagnostic and prognostic markers of EVD (57). Figure 2 collects current knowledge about important alterations in host cell miRNAs in various contexts (HUVECs, ARPE-19, Huh7, and NHPs. An investigation into v-miRNA production by EBOV during infection of human and bat cell lines via NGS revealed several non-coding RNAs (ncRNAs) from EBOV that were produced independently of the host cell-miRNA machinery. But confirmatory (immunological and molecular) analysis demonstrated that these ncRNAs were not associated with RISC and therefore did not function as miRNAs (58).

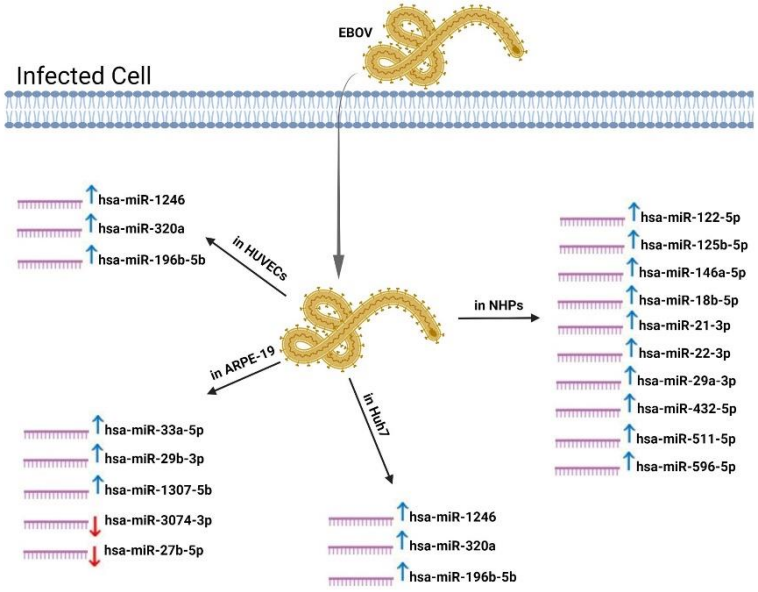

Fig. 2. Altered host-encoded miRNAs upon EBOV infection in different contexts. Following EBOV infection, certain cellular miRNAs are induced or repressed, leading to the regulation of multiple processes such as immune responses, cell cycle, apoptosis, etc. Indeed, these alterations in host miRNAs and the resulting cellular events constitute a pivotal part of EBOV pathogenesis. HUVECs: human umbilical vein endothelial cells, ARPE-19: human retinal pigment epithelial cell line, Huh7: human liver cell line, NHPs: non-human primates.

Most recently, an investigation has been conducted on the transcriptome of EBOV-infected cultured human liver cells, and a bioinformatic analysis showed that EBOV encoded two miRNAs (miR-MAY-251 and miR-MAK-403). At the verification step, the researchers indicated that miR-MAY-251 and miR-MAK-403 can potentially target several genes that play a role in viral replication, regulation of host cell immune response, and hemorrhagic symptoms in infected patients (59).

EBOV-miRNAs offer new opportunities for developing novel therapeutic strategies for EVD and biomarkers for early and accurate diagnosis of EVD, as well as for monitoring disease progression and response to treatment. They can also be targeted by antagomirs or mimics to modulate their expression and function, thereby altering the viral-host interaction and disease outcome. Furthermore, EBOV-miRNAs can be considered tools for studying the molecular mechanisms and pathogenesis of EVD, as well as for identifying new host factors and pathways involved in EBOV infection. The potential usability of EBOV-encoded miRNAs, including miR-VP-3p, miR-1-3p, miR-T3-3p, and miR-1-5p, as biomarkers for a better

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diagnosis and prognosis of EBOV-infected individuals (Figure 3). On the other hand, it has also been shown that EBOV-miR-1-5p, miR-T1-5p, miR-T2-3p, as well as anti-EBOV host cell miRNAs such as has-miR-150-3p, has-miR-103b, has-miR-15a-3p, has-miR-4692, has-miR-548-az, and has-miR-145-3p can be used as novel targets for more effective treatment of EVD patients. In conclusion, EBOV-miRNAs and host cellular miRNAs involved in EBOV infection might be important regulators of viral-host interaction and disease pathogenesis, and they provide new insights and avenues for EVD diagnosis and treatment. Although valuable studies have been done in fields of cellular and EBOV-miRNAs, further studies are needed to elucidate the details of related molecular mechanisms.

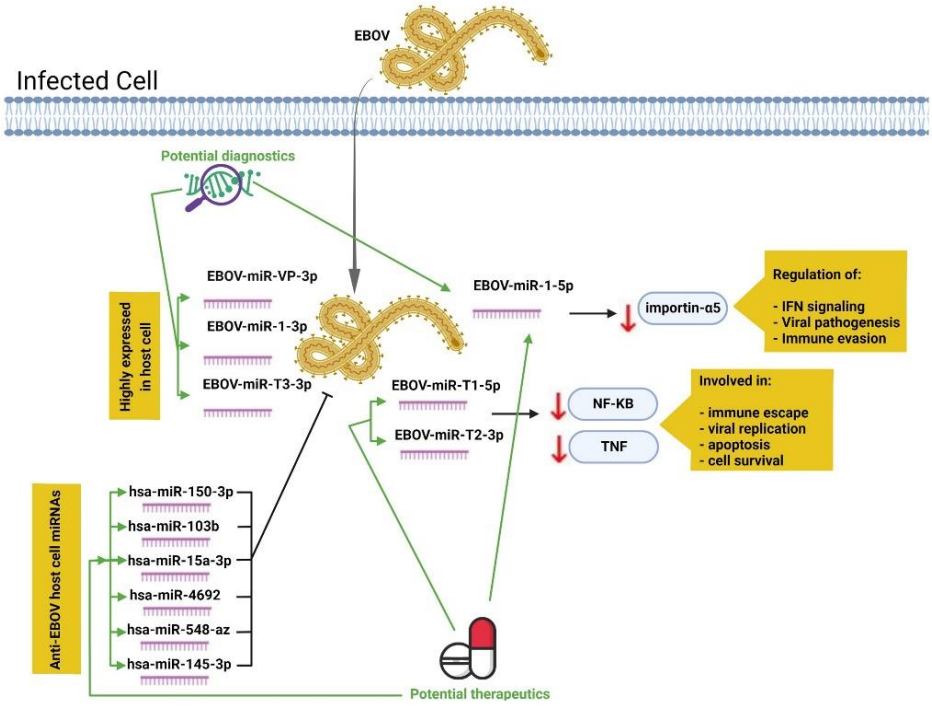

Fig. 3. EBOV-encoded miRNAs, role and their potential usability in the diagnostics and therapeutics of EVD. NF-KB: nuclear factor kappa B, TNF: tumor necrosis factor.

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