



International Journal of Molecular and Cellular Medicine p-ISSN: 2251-9637 o-ISSN: 2251-9645

A Review of the Interaction between miRNAs and Ebola Virus

Mohammad Shayestehpour^{3*}

- 1. Department of Virology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.
- 2. Applied Virology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran.
- 3. Department of Bacteriology and Virology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.

Article type:	ABSTRACT
Mini-review Article	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
Received:	for developing novel drugs against EVD and diagnostic panels for EBOV infection. EBOV-
2024.04.03	encoded miRNAs such as miR-VP-3p and miR-1-5p and anti-EBOV host cell miRNAs such
Revised:	as has-miR-150-3p, has-miR-103b and has-miR-145-3p might be a possible diagnostic
2024.07.01	biomarker or druggable targets. This paper highlights the importance of viral and cellular
Accepted:	miRNAs in EBOV infection and EVD.
2024.08.11	Keywords: Ebola virus, MicroRNAs, virus diseases

Cite this article: Kakavandi E, et al. A Review of the Interaction between miRNAs and Ebola Virus. International Journal of Molecular and Cellular Medicine. 2024; 13(2):210-219. DOI: 10.22088/IJMCM.BUMS.13.2.210

Address: Department of Bacteriology and Virology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran. E-mail: shayesteh2009@yahoo.co.uk



Publisher: Babol University of Medical Sciences

This work is published as an open access article distributed under the terms of the Creative Commons Attribution 4.0 License (http://creativecommons.org/licenses/by-nc/4). Non-commercial uses of the work are permitted, provided the original work is properly cited.

^{*}Corresponding: Mohammad Shayestehpour

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).

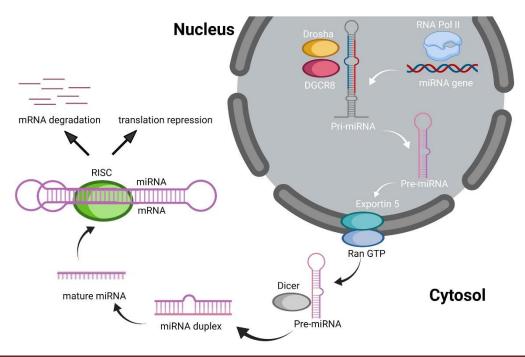


Fig. 1. miRNA biogenesis. RNA polymerase II produces a primary miRNA, or pri-miRNA. In the next step, pri-miRNA is matured by the DGCR8-Drosha complex, which is converted to pre-miRNA. The pre-miRNA is transported to the cytoplasm by Ran-GTP/exportin 5. In the cytosol, pre-miRNA is cleaved and converted 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.

[DOI: 10.22088/IJMCM.BUMS.13.2.210]

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-

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 hsamiR-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 miRNAlike 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-a5 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

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 hsamiR-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

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).

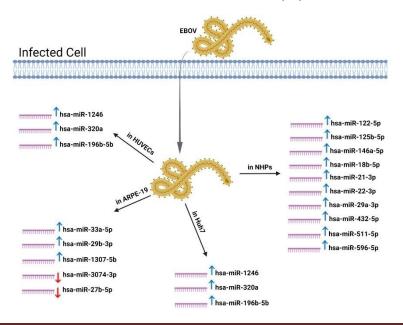


Fig. 2. Altered host-encoded miRNAs upon EBOV infection in different contexts. Following EBOV infection, certain cellular miRNAs are induced or repressed, leading to the regulation of multiple processes such as immune responses, cell cycle, apoptosis, etc. Indeed, these alterations in host miRNAs and 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

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.

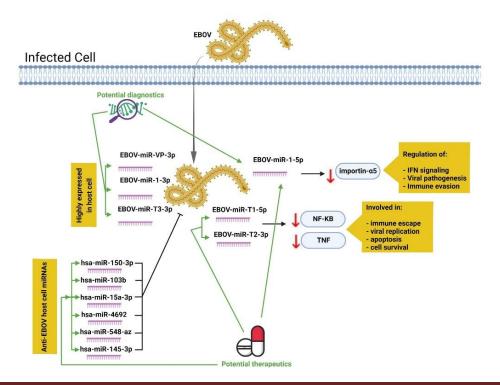


Fig. 3. EBOV-encoded miRNAs, role and their potential usability in the diagnostics and therapeutics of EVD. NF-KB: nuclear factor kappa B, TNF: tumor necrosis factor.

Funding

This research did not receive any specific grant form funding agencies in the public, commercial or not-for-profit sectors.

References

- 1. Carthew RW, Sontheimer EJ. Origins and mechanisms of miRNAs and siRNAs. Cell 2009;136:642-55.
- 2. Bartel DP. MicroRNAs: target recognition and regulatory functions. cell 2009;136:215-33.
- 3. Vidigal JA, Ventura A. The biological functions of miRNAs: lessons from in vivo studies. Trends Cell Biol 2015;25:137-47.
- 4. Wahid F, Shehzad A, Khan T, et al. MicroRNAs: synthesis, mechanism, function, and recent clinical trials. Biochim Biophys Acta Mol Cell Res 2010;1803:1231-43.

- 5. Zhang J, Li S, Li L, et al. Exosome and exosomal microRNA: trafficking, sorting, and function. Genom Proteom Bioinf 2015;13:17-24.
- 6. Shayestehpour M, Moghim S, Salimi V, et al. Targeting human breast cancer cells by an oncolytic adenovirus using microRNA-targeting strategy. Virus Res 2017;240:207-14.
- 7. Shayestehpour M, Moghim S, Salimi V, et al. Selective replication of miR-145-regulated oncolytic adenovirus in MCF-7 breast cancer cells. Future Virol 2016;11:671-80.
- 8. Kakavandi E, Shayestehpour M, Moghim S. Cancer virotherapy: Targeting cancer cells by microRNA mechanism for selective replication of oncolytic viruses in these cells. Koomesh journal 1401;24:288-99.
- 9. Sadri Nahand J, Moghoofei M, Salmaninejad A, et al. Pathogenic role of exosomes and microRNAs in HPV-mediated inflammation and cervical cancer: a review. Int j cancer 2020;146:305-20.
- 10. Lajer CB, Garnaes E, Friis-Hansen L, et al. The role of miRNAs in human papilloma virus (HPV)-associated cancers: bridging between HPV-related head and neck cancer and cervical cancer. Br j Cancer 2012;106:1526-34.
- 11. Farzanehpour M, Mozhgani SH, Jalilvand S, et al. Serum and tissue miRNAs: potential biomarkers for the diagnosis of cervical cancer. Virol J 2019;16:1-9.
- 12. Buzdin AA, Artcibasova AV, Fedorova NF, et al. Early stage of cytomegalovirus infection suppresses host microRNA expression regulation in human fibroblasts. Cell Cycle 2016;15:3378-89.
- 13. Lee KH, Lim BJ, Ferreira VH, et al. Expression of human miR-200b-3p and-200c-3p in cytomegalovirus-infected tissues. Biosci Rep 2018;38.
- 14. Fu M, Gao Y, Zhou Q, et al. Human cytomegalovirus latent infection alters the expression of cellular and viral microRNA. Gene 2014;536:272-8.
- 15. Zhang Gl, Li YX, Zheng Sq, et al. Suppression of hepatitis B virus replication by microRNA-199a-3p and microRNA-210. Antivir Res 2010:88:169-75.
- 16. Zhang Y, Jia Y, Zheng R, et al. Plasma microRNA-122 as a biomarker for viral-, alcohol-, and chemical-related hepatic diseases. Clin chem 2010:56:1830-8.
- 17. Ma YJ, Yang J, Fan XL, et al. Cellular micro RNA let-7c inhibits M1 protein expression of the H1N1 influenza A virus in infected human lung epithelial cells. J Cell Mol Med 2012;16:2539-46.
- 18. Tomita M, Tanaka Y, Mori N. MicroRNA miR-146a is induced by HTLV-1 tax and increases the growth of HTLV-1-infected T-cells. Int J Cancer 2012;130:2300-9.
- 19. Pichler K, Schneider G, Grassmann R. MicroRNA miR-146a and further oncogenesis-related cellular microRNAs are dysregulated in HTLV-1-transformed T lymphocytes. Retrovirology 2008;5:1-12.
- 20. Sun G, Li H, Wu X, et al. Interplay between HIV-1 infection and host microRNAs. Nucleic Acids Res 2012;40:2181-96.
- 21. Jopling CL, Yi M, Lancaster AM, et al. Modulation of hepatitis C virus RNA abundance by a liver-specific MicroRNA. science 2005;309:1577-81.
- 22. Umbach JL, Cullen BR. The role of RNAi and microRNAs in animal virus replication and antiviral immunity. Genes Dev 2009;23:1151-64.
- 23. Lo AKF, To KF, Lo KW, et al. Modulation of LMP1 protein expression by EBV-encoded microRNAs. Proc Natl Acad Sci 2007;104:16164-9.
- 24. Kaul D, Ahlawat A, Gupta SD. HIV-1 genome-encoded hiv1-mir-H1 impairs cellular responses to infection. Mol Cell Biochem 2009:323:143-8.

- 25. Diggins NL, Hancock MH, editors. Viral miRNA regulation of host gene expression. Seminars in Cell & Developmental Biology; 2023: Elsevier.
- 26. Gouzouasis V, Tastsoglou S, Giannakakis A, et al. Virus-derived small rnas and microRNAs in health and disease. Annu Rev Biomed Data Sci 2023;6:275-98.
- 27. Kuhn JH, Amarasinghe GK, Basler CF, et al. ICTV virus taxonomy profile: Filoviridae. J Gen Virol 2019;100:911.
- 28. Jacob ST, Crozier I, Fischer WA, et al. Ebola virus disease. Nat Rev Dis Primers 2020;6:13.
- 29. ICTV. Genus: Ebolavirus. 2021; Available from: https://talk.ictvonline.org/ictv-reports/ictv_online_report/negative-sense-rna-viruses/ w/filoviridae/1086/genus-ebolavirus.
- 30. WHO. Ebola virus disease WHO | World Health Organization. 2021; Available from: https://www.who.int/news-room/fact-sheets/ detail/ebola-virus-disease.
- 31. WHO. WHO Ebola Situation Report 10 June 2016. 2016; Available from: http://apps.who. int/iris/bitstream/ handle/10665/208883/ebolasitrep_10Jun2016_eng.pdf;jsessionid=59D3FDEB686F6160AFB252D7386118DA?sequence=1.
- 32. Hussain M, Torres S, Schnettler E, et al. West Nile virus encodes a microRNA-like small RNA in the 3' untranslated region which up-regulates GATA4 mRNA and facilitates virus replication in mosquito cells. Nucleic Acids Res 2012;40:2210-23.
- 33. Hussain M, Asgari S. MicroRNA-like viral small RNA from Dengue virus 2 autoregulates its replication in mosquito cells. Proceedings of the National Academy of Sciences 2014;111:2746-51.
- 34. Perez JT, Varble A, Sachidanandam R, et al. Influenza A virus-generated small RNAs regulate the switch from transcription to replication. Proc Natl Acad Sci 2010;107:11525-30.
- 35. Umbach JL, Yen HL, Poon LLM, et al. Influenza A virus expresses high levels of an unusual class of small viral leader RNAs in infected cells. MBio 2010;1:e00204-10.
- 36. Li X, Fu Z, Liang H, et al. H5N1 influenza virus-specific miRNA-like small RNA increases cytokine production and mouse mortality via targeting poly (rC)-binding protein 2. Cell Res 2018;28:157-71.
- 37. Liang H, Zhou Z, Zhang S, et al. Identification of Ebola virus microRNAs and their putative pathological function. Sci China Life Sci 2014;57:973-81.
- 38. Nyakarahuka L, Kankya C, Krontveit R, et al. How severe and prevalent are Ebola and Marburg viruses? A systematic review and meta-analysis of the case fatality rates and seroprevalence. BMC Infect Dis 2016;16:1-14.
- 39. Simmons G, Wool-Lewis RJ, Baribaud F, et al. Ebola virus glycoproteins induce global surface protein down-modulation and loss of cell adherence. J Virol 2002;76:2518-28.
- 40. Peters CJ, Peters JW. An introduction to Ebola: the virus and the disease. J Infect Dis 1999;179:ix-xvi.
- 41. Kakayandi E, Shahbahrami R, Goudarzi H, et al. Anoikis resistance and oncoviruses. J Cell Biochem 2018;119:2484-91.
- 42. Sheng M, Zhong Y, Chen Y, et al. Hsa-miR-1246, hsa-miR-320a and hsa-miR-196b-5p inhibitors can reduce the cytotoxicity of Ebola virus glycoprotein in vitro. Sci China Life Sci 2014;57:959-72.
- 43. Teng Y, Wang Y, Zhang X, et al. Systematic genome-wide screening and prediction of microRNAs in EBOV during the 2014 Ebolavirus outbreak. Sci Rep 2015;5:1-17.
- 44. Golkar Z, Battaria R, Pace DG, et al. Inhibition of Ebola virus by anti-Ebola miRNAs in silico. J Infect Dev Countr 2016;10: 626-34.
- 45. Chen Z, Liang H, Chen X, et al. An Ebola virus-encoded microRNA-like fragment serves as a biomarker for early diagnosis of Ebola virus disease. Cell Res 2016;26:380-3.
- 46. Katze MG, He Y, Gale M. Viruses and interferon: a fight for supremacy. Nat Rev Immunol 2002;2:675-87.

- 47. Hoffmann HH, Schneider WM, Rice CM. Interferons and viruses: an evolutionary arms race of molecular interactions. Trends immunol 2015;36:124-38.
- 48. García-Sastre A. Ten strategies of interferon evasion by viruses. Cell Host Microbe 2017;22:176-84.
- 49. Reid SP, Leung LW, Hartman AL, et al. Ebola virus VP24 binds karyopherin α1 and blocks STAT1 nuclear accumulation. J Virol 2006:80:5156-67.
- 50. Liu Y, Sun J, Zhang H, et al. Ebola virus encodes a miR-155 analog to regulate importin-α5 expression. Cell Mol Life Sci 2016;73:3733-44.
- 51. Duy J, Koehler JW, Honko AN, et al. Circulating microRNA profiles of Ebola virus infection. Sci Rep 2016;6:1-13.
- 52. Wang Z, Li J, Fu Y, et al. A rapid screen for host-encoded miRNAs with inhibitory effects against ebola virus using a transcription-and replication-competent virus-like particle system. Int J Mol Sci 2018;19:1488.
- 53. Duy J, Honko A, Altamura LA, et al. Virus-encoded miRNAs in Ebola virus disease. Sci Rep 2018;8:1-14.
- 54. Forrester JV, Xu H, Lambe T, et al. Immune privilege or privileged immunity? Mucosal immunol 2008;1:372-81.
- 55. Oliver GF, Orang AV, Appukuttan B, et al. Expression of microRNA in human retinal pigment epithelial cells following infection with Zaire ebolavirus. BMC Res notes 2019;12:1-7.
- 56. Diallo I, Ho J, Laffont B, et al. Altered microRNA Transcriptome in Cultured Human Liver Cells upon Infection with Ebola Virus. Int J MolSci 2021;22:3792.
- 57. Stefan CP, Arnold CE, Shoemaker CJ. Transcriptomic Analysis Reveals Host miRNAs Correlated with Immune Gene Dysregulation during Fatal Disease Progression in the Ebola Virus Cynomolgus Macaque Disease Model. Microorganisms 2021;9:665.
- 58. Prasad AN, Ronk AJ, Widen SG. Ebola virus produces discrete small noncoding RNAs independently of the host microRNA pathway which lack RNA interference activity in bat and human cells. J Virol 2020;94:e01441-19.
- 59. Diallo I, Husseini Z, Guellal S, et al. Ebola Virus Encodes Two microRNAs in Huh7-Infected Cells. Int J Mol Sci 2022;23:5228.