REVIEW

microRNAs and the Ebola Virus

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Received: December 23, 2014
Published: May 11, 2015

We recently reported an interesting finding that the Ebola virus (EBOV) encodes functional microRNAs (miRNAs) that can be produced through the host's miRNA processing machinery. Furthermore, prediction of EBOV miRNA target genes provided some clues about the regulatory roles of EBOV miRNAs. In summary, our study paves the road for further investigating the roles of EBOV miRNAs in viral infection and virus-host interactions.

Keywords: microRNA; Ebola Virus

To cite this article: Zheng Fu, et al. microRNAs and the Ebola Virus. RNA Dis 2015; 2: e492. doi: 10.14800/rd.492.

Ebola virus (EBOV) is a type of filovirus with an enveloped negative-sense RNA genome. EBOV usually causes severe and lethal infections in humans and primates [1]. The Ebola virus disease (EVD) has a high risk of death, killing 50%-90% of infected patients [1]. Recently, the outbreak of EVD in West Africa brought international attention to the virus [2]. As of December 14th 2014, there have been 18,603 reported EBOV cases in eight countries since the beginning of the outbreak, with 6,915 reported deaths according to the WHO. Currently, no effective treatment or diagnostic method for EVD is available [3], and the detailed molecular mechanisms underlying EBOV infection, immune evasion, pathogenesis, and host interaction are far from clear.

microRNAs (miRNAs) are a class of small non-coding RNAs that play pivotal roles in a variety of physiological processes [4, 5]. miRNAs are not only found in eukaryotes but are also transcribed by various viruses to manipulate their own genes and/or the hosts' genes [6, 7], and they are believed to be important regulators of the virus-host interaction and key elements in viral pathogenesis [8]. At present, most of the known viral miRNAs have been identified to be encoded by DNA viruses, because DNA viruses replicate in the nucleus and thus can hijack the host's miRNA processing machinery. In contrast, RNA viruses replicate in the cytoplasm and have no access to the host's miRNA processing machinery [9]. Therefore, the capacity of RNA viruses to encode miRNAs has previously been neglected.

Despite these preconceived notions, recent studies have confirmed that laboratory-engineered RNA viruses (e.g., Sindbis virus, vesicular stomatitis virus, and influenza virus) are able to express miRNA-like small RNAs [10-14]. In addition, several retroviruses (e.g., human immunodeficiency virus, bovine leukemia virus, and several cytoplasmic RNA viruses), were found to encode miRNAs, although the underlying mechanisms remain unclear. It was further confirmed that the EBOV VP35 protein had the ability to suppress RNA silencing, which provides a clue about the link between EBOV and miRNAs [15, 16]. Furthermore, it was reported that the expression of three endogenous miRNAs was increased in human umbilical vein endothelial cells upon infection with EBOV GP-expressing adenovirus [17]. This study not only provides important evidence for understanding the human-EBOV interaction but also offers some clues about the indispensable contribution of miRNA to the virulence of EBOV.

In our recent study, we hypothesized that the genome of EBOV could produce miRNAs using the host's miRNA processing system [18]. To investigate this possibility, we used a strategy that combined bioinformatic analysis and experimental validation to search for putative EBOV miRNAs. We identified two putative viral miRNA precursors and three putative mature miRNAs derived from the EBOV genome. The miRNAs were found to be Dicer-dependent and functionally active in vitro. The results of a cellular target prediction analysis indicated that EBOV miRNAs could regulate various host genes involved in virus-host interaction, immune escape, and cell apoptosis [18], which may explain how EBOV can duplicate massively without being detected by the host immune system and cause severe hemorrhagic fever symptoms. Interestingly, we found that the Reston EBOV strain did not encode these miRNAs, in contrast to the Sudan and Zaire EBOV strains, which have high pathogenicity and mortality rates in humans. This may explain, at least in part, the non-pathogenicity of Reston EBOV to humans.

Taken together, our study provides evidence to support the hypothesis that EBOV, as an RNA virus, is capable of encoding functional miRNAs via the host's miRNA processing machinery. Our findings pave the road for further investigating the roles of the EBOV miRNAs during viral infection and virus-host interactions. Furthermore, our findings may have some clinical applications. The detection of circulating EBOV miRNAs in human blood may provide an effective tool for the diagnosis of EBOV infection, considering that specific miRNAs encoded by infectious virus have been detected in human blood samples and can serve as sensitive and specific indicators for virus infection. The advantage of EBOV miRNAs as non-invasive biomarkers guarantees the accuracy and promptness of the detection of disease, which can enable fast isolation and early treatment, prevent the spread of the virus, and increase the survival opportunity of the patients. As for the treatment of EBOV disease, miRNA may also be a promising target. Specific treatments targeting EBOV miRNAs may impede the virus' immune evasion, reactivate immune surveillance and induce pathogen elimination. Future work will evaluate the sensitivity, specificity, and accuracy of this approach by assessing EBOV miRNAs in blood samples from EBOV-infected patients. Future studies should also be focused on investigating the targets and pathogenic mechanisms of EBOV miRNAs. We believe that the investigation of miRNAs may provide a turning point that allows us to uncover the mechanisms of EBOV pathogenesis and immune evasion and elucidate the intricate relationship between the virus and human beings.

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